$TiCl_4$-Mediated Direct N-Alkylation of Sulfonamides with Inactive Ethers

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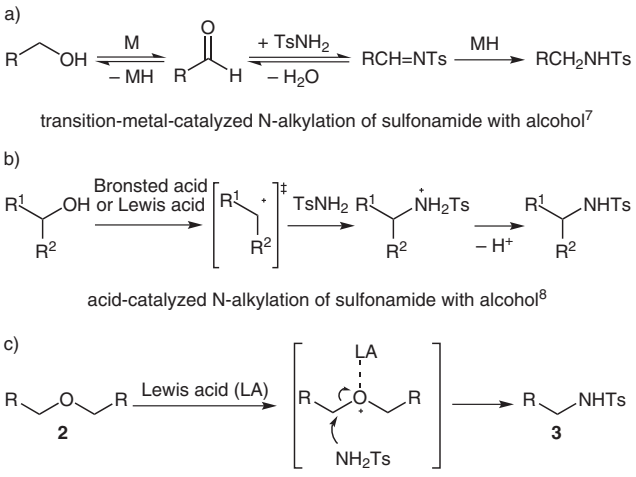
Abstract: A $TiCl_4$-mediated intermolecular or intramolecular direct N-alkylation reaction of sulfonamides with inactive ethers as alkylating agents was successfully achieved. This method provides a novel approach towards *N*-alkyl sulfonamides from inactive ethers via an easy workup procedure.

Key words: N-alkylation, Lewis acid, *N*-alkyl sulfonamide, dialkyl ether, titanium tetrachloride

The development of new methodologies for the formation of carbon–nitrogen bonds is a challenging area of organic synthesis.[1] In this context, N-alkylation reactions of sulfonamides have attracted significant attention, because *N*-alkyl sulfonamides exhibit a wide range of biological activities, such as antibacterial, anticancer and antiviral functions, and they serve as antiviral HIV protease inhibitors.[2] Generally, the classical method for the synthesis of N-alkylated sulfonamides are performed by the reaction of amines with sulfonyl halides,[3] and transition-metal-catalyzed cross-coupling of sulfonamides with organic halides or olefins.[4] Recently, N-alkylation of sulfonamide using alcohol as alkylating agent has attracted particularly interest due to the easy activation of the hydroxyl group by transition metal salts or small organic molecules. For example, Beller and Williams et al. found transition metals Ru(III) or Cu(II) could efficiently catalyze the N-alkylation of sulfonamide using borrowing hydrogen methodology (Scheme 1, a).[5] Of course, besides Fukuyama–Mitsunobu N-alkylation,[6] much progress on acid-catalyzed direct N-alkylation with alcohol has also been achieved. Various Lewis acids and Brønsted acids have been employed to realize this transformation via a carbocation mechanism (Scheme 1, b).[7] Considering the widespread application of N-alkylated sulfonamide in the synthesis of pharmaceuticals and agrochemicals, the exploration of new direct N-alkylation of sulfonamides using various alkylating agents under mild conditions is always desirable.

As we know, compared with alcohol alkylating agent, the activation of sp^3 C–O bond in aliphatic ether is much more challenging which is arising from the high bond energy,[8] and the N-alkylation of amides with ethers are rarely studied.[9] Nevertheless, we think that a suitable catalyst could also possibly activate the carbon–oxygen single bond of an ether via the coordination with the ether oxygen atom, then enhance the nucleophilic attack of the amide nitrogen at the ether carbon atoms to produce N-alkylating sulfonamides **3** (Scheme 1, c). In connection with our interest in the development of N-acylation and N-alkylation of sulfonamide,[10] we report herein a novel $TiCl_4$-promoted N-alkylation of sulfonamides using inactive ethers as alkylating reagents.



Scheme 1 N-alkylation of sulfonamide

N-Alkylation of 4-toluene sulfonamide (0.5 mmol) with ether was first succeeded with boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$, 2.0 equiv) in dry toluene (1.0 mL) at 110 °C. It is believed that the coordination of the ether oxygen to the boron atom activates the carbon–oxygen bonds of ether for the nucleophilic attack. To our delight, we found BF_3 could promote the N-alkylation of sulfonamide with diethyl ether to form *N*-alkyl sulfonamide **3a** (38% yield) and *N*,*N*-dialkyl sulfonamide **3aa** (11% yield, Table 1, entry 1). Inspired by this positive result, we further investigated other reaction conditions to define the reaction parameters, and found that a reaction time of 48 hours and 6.0 equiv of $BF_3{\cdot}OEt_2$ gave **3a** and **3aa** in a total yield of 95% (Table 1, entry 6). Increasing the promoter loading further did not improve the yields (Table 1, compare entries 6, 7, and 8). When the reaction temperature was lowered to 90 °C or increased to 130 °C, the yield decreased due to the incomplete reaction or tedious workup, respectively (Table 1, compare entries 6 and 9, 10). The effect of the solvent was also investigated, toluene and ethyl acetate were the better solvents, with 1,1,2,2-tetra-

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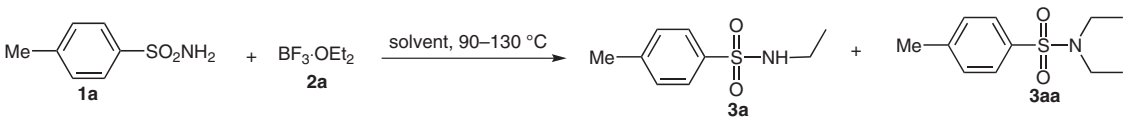
chloroethane (TCE) being the best (Table 1, compare entries 6 and 11–15).

Unfortunately, when we attempted to extend this reaction to other dialkyl ethers such as di-*n*-butyl ether using $BF_3{\cdot}OEt_2$ (6.0 equiv) as promoter, only 36% yield of *N*-*n*-butyl *p*-toluene sulfonamide (**3b**) was obtained due to a possible weak complexation between BF_3 and di-*n*-butyl ether (Table 2, entry 11), so we turned our efforts to screen other Lewis acid promoters including $AlCl_3$, $FeCl_3$, $TiCl_4$, $ZrCl_4$, MgO, etc. to get satisfying conversion, and the corresponding results are summarized in Table 2. As shown in Table 2, among the tested Lewis acids, $TiCl_4$ showed the most effective promotion of mono-N-alkylation of sulfonamide with di-*n*-butyl ether in 60% yield (Table 2, entry 5), and basically other Lewis acids could not afford good yields of the desired product **3b** (Table 2, entries 1–11). We tried to use an excess amount of dialkyl ether with respect to sulfonamide and extended the reaction time (48 h) in order to further improve the yield of the transformation, and finally the best yield of **3b** (78%) was achieved in the presence of $TiCl_4$ (6.0 equiv) at 120 °C for 48 hours when the ratio of **2b/1a** is 12:1(Table 1, compare entries 12–14). Noteworthy, if the reaction time was further extended to 72 hours, the yield of monoalkylation product **3b** would decrease to some degree due to the formation of N,N-dialkylated product (Table 2, entry 14).

Accordingly, the substrate scope for the mono-N-alkylation of sulfonamides was further extended to various ethers using the optimized reaction conditions.[11] As shown in Table 3, the alkylating reagents examined could be performed smoothly in moderate to good yields. Analysis of the efficiency in which our substrates are N-alkylated indicates that both electronic and steric effects govern the N-alkylation system. Increasing the electronic density of the sulfonamide nitrogen enhance the N-alkylation performance (Table 3, entries 1–5), while electronic-

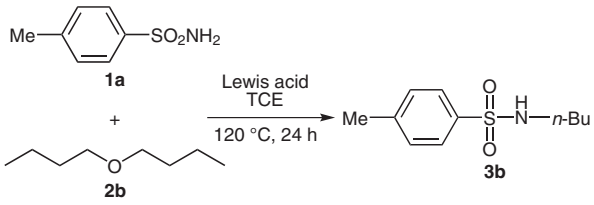
Table 1 BF_3-Promoted N-Alkylation of *p*-Toluenesulfonamide (**1a**) with Diethyl Ether as Alkylating Agent[a]



Entry	$BF_3{\cdot}OEt_2$ (equiv)	Temp (°C)	Solvent	Product (%)[b]		
				3a	**3aa**	Total yield
1	2	110	toluene	38	11	49
2	3	110	toluene	40	37	77
3	4	110	toluene	40	36	76
4	6	110	toluene	45	46	91
5	6	110	toluene	54[c]	34[c]	88
6	6	110	toluene	39[d]	56[d]	95
7	7	110	toluene	48	31	79
8	8	110	toluene	44	40	84
9	6	90	toluene	40	7	47
10	6	130	toluene	46	41	87
11	6	120	TCE	38	56	94
12	6	80	EtOAc	41	36	77
13	6	90	DCE	54	10	64
14	6	150	DMSO	–	–	–
15	6	110	MeCN	trace	trace	trace

[a] Reaction conditions: all reactions were carried out under an Ar atmosphere in a sealed tube, sulfonamide (0.5 mmol), solvent (1.0 mL), 24 h.
[b] Isolated yield after purification.
[c] Reaction time: 18 h.
[d] Reaction time: 48 h.

Table 2 Catalyst Screening for Mono-N-alkylation of *p*-Toluene Sulfonamide with Di-*n*-butyl Ether as Alkylating Agent[a]



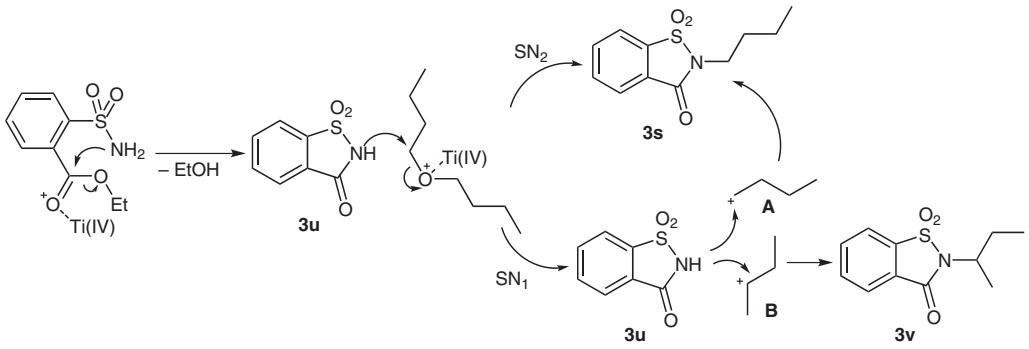
Entry	Catalyst	Reaction time (h)	Yield (%)[b,c]
1	$AlCl_3$	24	24
2	$FeCl_3$	24	23
3	Fe_2O_3	24	n.r.
4	$ZrCl_4$	24	9
5	$TiCl_4$	24	60
6	MgO	24	n.r.
7	$Cu(OAc)_2·H_2O$	24	n.r.
8	$FeCl_2·4H_2O$	24	n.r.
9	$CdCl_2·2.5H_2O$	24	n.r.
10	$NiCl_2·6H_2O$	24	n.r.
11	$BF_3·OEt_2$	24	36
12	$TiCl_4$	24	69[d]
13	$TiCl_4$	48	78[d]
14	$TiCl_4$	72	70[e]

[a] Reaction conditions: *p*-toluene sulfonamide (0.5 mmol), di-*n*-butyl ether (6.0 equiv, 3.0 mmol), Lewis acid (6.0 equiv), TCE (1.0 mL), the reaction was carried out at 120 °C at the given reaction time in sealed tube.
[b] Isolated yield after purification.
[c] n.r. = no reaction
[d] Conditions: 12.0 equiv of di-*n*-butyl ether were used.
[e] Conditions: 24.0 equiv of di-*n*-butyl ether were used.

deficient substrates leads to decreased product yield (Table 3, entry 6), and the similar electronic effect of substituents on the dibenzyl ethers was also observed (Table 3, entries 7–9). Steric-hindrance effects also play a key role in this reaction system, as increasing the steric hindrance of the ether at C_a leads to a substantial decrease in product yield, while decreasing the steric hindrance at C_a leads to an improved N-alkylating yield (Table 3, compare entries 1 and 11, 12), but for the N-substituted sulfonamide **1g**, no significant steric effect was observed (Table 3, compare entries 1 and 15). It is interesting to note that when we employed diethyl ether as alkylating agent using $BF_3·OEt_2$ as promoter, the N-alkylation product of *N*-phenyl-*p*-toluene sulfonamide (**1h**) is toluene-4-sulfonic acid ethyl ester (**3p**, 69% yield) instead of *N*-ethyl-*N*-phenyl-4-methyl-benzenesulfonamide (Table 3, entry 16), possibly due to the large steric hindrance effect from N-substituted amide that favors esterlysis of sulfonamide. Changing the substrate from an aryl sulfonamide to an alkyl sulfonamide, such as methanesulfonamide, also gave the desired alkylated product **3q** in 56% yield (Table 3, entry 17). Moreover, if *p*-toulene sulfonamide (**1a**) was treated upon the unsymmetrical ether methoxymethylbenzene (**2f**), the alkylation reaction would only afford *N*-benzyl-4-methyl-benzensulfonamide (**3h**, 40% yield) without detectable byproducts *N*-methyl-4-methyl-benzensulfonamide (Table 3, entry 10). Although $TiCl_4$ could promote 2-(ethoxymethyl) benzenesulfonamide to form 2,3-dihydro-benzo[*d*]isothiazole 1,1-dioxide (**3r**) via intramolecular N-alkylation, the corresponding yield is poor (Table 3, entry 18).

To our satisfaction, $TiCl_4$ could enhance 2-sulfamonylbenzoic acid ethyl ester (**1k**) to form unexpected cyclic N-alkylation product 2-*n*-butyl-1,1-dioxo-1,2-dihydro-1λ⁶-benzo[*d*] isothiazo-3-one (**3s**) and 2-benzyl-1,1-dioxo-1,2-dihydro-1λ⁶-benzo[*d*] isothiazo-3-one (**3t**) in good yield (Table 3, entries 19 and 20). A possible reaction pathway for **3s** is depicted in Scheme 2. The ester carbonyl group was activated by an initial coordination of the carbonyl oxygen with Ti(IV), and suffered an intramolecular nucleophilic attack from sulfonamide nitrogen to generate the N-acylation product **3u**,[10] and the corresponding amide nitrogen continued to attack the ether–oxygen bond activated by Ti(IV) via SN_2 displacement, and led to the formation of N-alkylation product **3s**. During the N-alkylation reaction of **1k**, the rearranged product **3v** was not detected using GC–MS method, so the S_N1 transformation pathway was excluded.

In conclusion, we have demonstrated that the direct intermolecular or intramolecular N-alkylation of sulfonamides with inactive esters is possible using $TiCl_4$ as promoter for



Scheme 2 Mechanistic proposal for the $TiCl_4$-promoted cascade N-acylation/N-alkylation of sulfonamide **1k**

the first time. This transformation may be of interest in the synthesis of complex cyclic polyfunctionalized sulfonamides.

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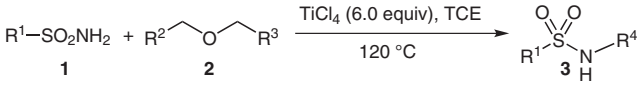
Table 3 $TiCl_4$-Catalyzed N-Alkylation of Sulfonamides with Ethers



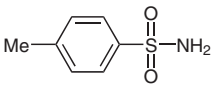
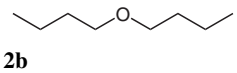
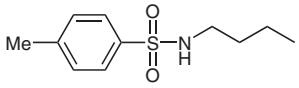
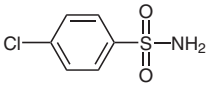
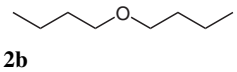
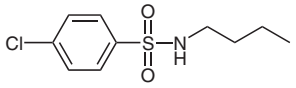
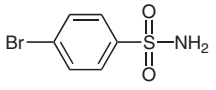
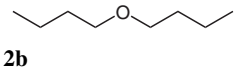
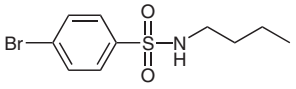
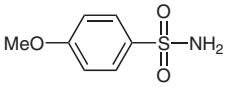
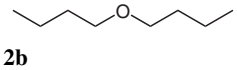
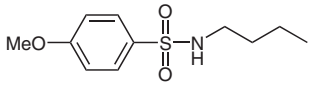
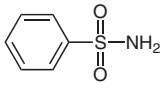
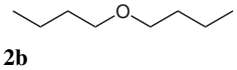
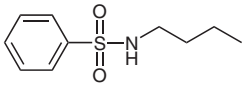
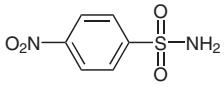
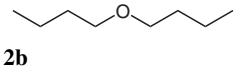
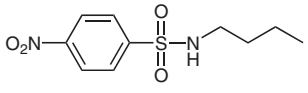
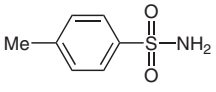
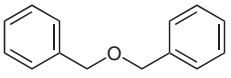
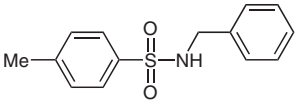
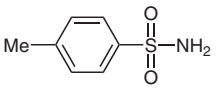
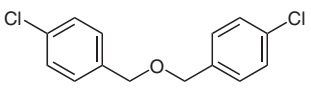
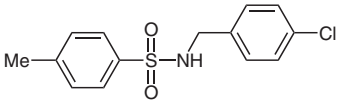
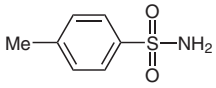
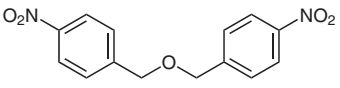
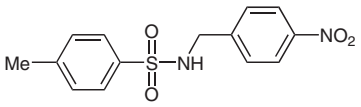
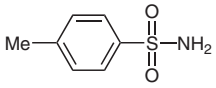
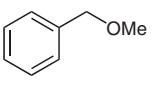
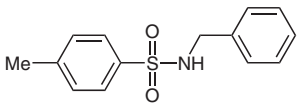
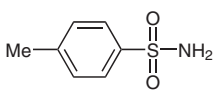
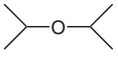
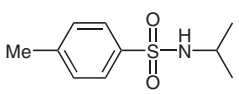
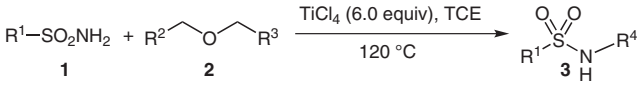
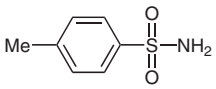
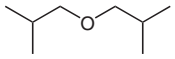
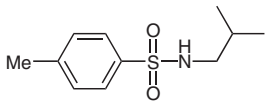
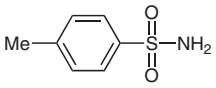
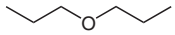
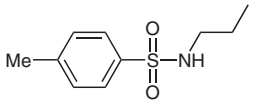
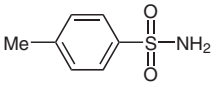
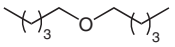
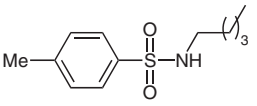
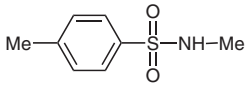
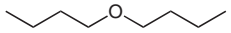
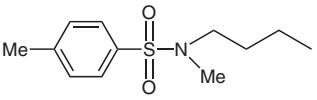
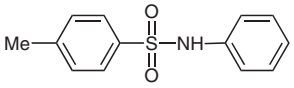
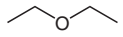
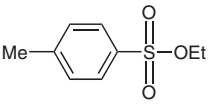
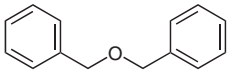
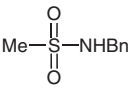
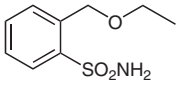
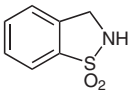
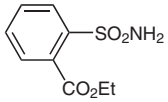
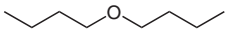
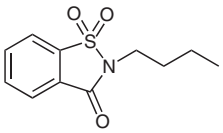
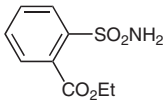
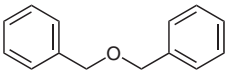
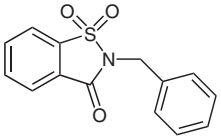
Entry	Sulfonamide	Ether	Time (h)	Product	Yield (%)[a,b]
1	 **1a**	 **2b**	48	 **3b**	78
2	 **1b**	 **2b**	24	 **3c**	73
3	 **1c**	 **2b**	48	 **3d**	75
4	 **1d**	 **2b**	72	 **3e**	79
5	 **1e**	 **2b**	48	 **3f**	80
6	 **1f**	 **2b**	48	 **3g**	39
7	 **1a**	 **2c**	48	 **3h**	69
8	 **1a**	 **2d**	24	 **3i**	49
9	 **1a**	 **2e**	48	 **3j**	–
10	 **1a**	 **2f**	48	 **3h**	40
11	 **1a**	 **2g**	48	 **3k**	40

Table 3 $TiCl_4$-Catalyzed N-Alkylation of Sulfonamides with Ethers (continued)



Entry	Sulfonamide	Ether	Time (h)	Product	Yield (%)[a,b]
12	 **1a**	 **2h**	48	 **3l**	33
13	 **1a**	 **2i**	48	 **3m**	61
14	 **1a**	 **2j**	48	 **3a**	79
15	 **1g**	 **2b**	48	 **3o**	77
16	 **1h**	 **2k**	48	 **3p**	69[c]
17	$MeSO_2NH_2$ **1i**	 **2c**	48	 **3q**	56[d]
18	 **1j**	–	48	 **3r**	18[e]
19	 **1k**	 **2b**	48	 **3s**	64
20	 **1k**	 **2c**	24	 **3t**	69

[a] Isolated yields, average of 2 runs.
[b] Reaction conditions: *p*-toluene sulfonamide (0.5 mmol), ether (12.0 equiv, 6.0 mmol), Lewis acid (6.0 equiv, 3.0 mmol), TCE (2.0 mL), the reaction was carried out at 120 °C at the given reaction time in sealed tube.
[c] $BF_3{\cdot}OEt_2$ (6.0 equiv) was used.
[d] The reaction was carried out at 90 °C.
[e] Lowering the reaction temperature (≤120 °C) or increasing the reaction temperature (≥120 °C) resulted in poorer yield.

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(11) **General Procedure for the Transformation**
Sulfonamide (0.50 mmol), ether (12.0 equiv, 6.0 mmol) and $Cl_2CHCHCl_2$ (2.0 mL) were combined in a pressure tube equipped with a stir bar, the mixture was stirred about 10 min, then $TiCl_4$ (6.0 equiv, 3.0 mmol) was added, and the reaction mixture was heated to 120 °C for the given time. After the starting material has disappeared (monitored by TLC), the reaction mixture was cooled to r.t. and treated with H_2O (5.0 mL) to decompose the exceed $TiCl_4$, then filtered, and the filtrate was extracted with EtOAc (3 × 10 mL). The combined organic layers was dried over Na_2SO_4 and concentrated in vacuo, the corresponding residue was purified by flash column chromatography (silica gel) to furnish the target product. All the products are known compounds and are identified using ^1H NMR, LRMS, and IR by comparison with previously reported data (see Supporting Information for complete details).

