N-Alkoxymethylation of Secondary Amides, Sulfonamides and Phosphamides Using Dialkoxymethanes in the Presence of Lewis Acids

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Abstract: A convenient and efficient one-pot synthesis of *N*-alkoxymethyl derivatives of secondary amides, sulfonamides and phosphamides in reaction with the appropriate dialkoxymethanes in the presence of a Lewis acid is described. In this method the use of toxic and carcinogenic chloromethyl alkyl ethers was eliminated.

Key words: acetals, amides, heterocycles, protecting groups, sulfonamides

Alkoxymethyl groups, especially the methoxymethyl group, play important role in organic synthesis. They are employed both as protecting groups[1] and as a structural element of many chemical compounds of considerable interest, e.g. *N*-(alkoxymethyl)-2-chloroacetanilide derivatives, which are manufactured as commercial herbicides, e.g. Alachlor® (**1**, $R^1 = CH_2Cl$, $R^2 = CH_3$, $R^3 = R^4 = C_2H_5$, Figure 1).[2–6]

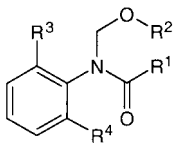

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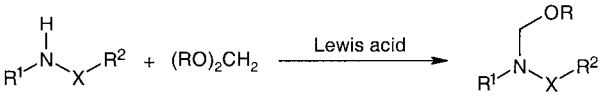
Figure 1

There are a few methods to synthesize compounds bearing an alkoxymethyl moiety at a nitrogen atom. Usually, they are prepared in several steps starting from the appropriate amines and formaldehyde.[7,8] These reactions involve intermediate *N*-acyliminium salts, which are not easy to handle.[9] Another useful method consists of the alkylation of amides with the corresponding alkoxymethyl chlorides.[10] However, alkoxymethyl chlorides other than methoxymethyl chloride are not easily available, so this method is convenient only for the preparation of methoxymethyl derivatives. In our previous paper[11] we have shown that the latter can be easily converted into other *N*-alkoxymethyl derivatives by heating with an appropriate alcohol in the presence of catalytic amounts of *p*-toluenesulfonic acid.

The main drawback of syntheses with chloromethyl methyl ether is the high toxicity of this reagent, which has been proved to be a strong carcinogen.[12] Looking for synthetic equivalents of chloromethyl methyl ether we turned our attention on dimethoxymethane. This cheap, commercially available and easy to handle reagent proved to be an excellent source of the methoxymethyl group. In the present paper we would like to report a simple one-pot alkoxymethylation of secondary amides, sulfonamides and phosphamides using dimethoxymethane and diethoxymethane in the presence of a Lewis acid.

A few preliminary attempts to introduce an alkoxymethyl group at a nitrogen atom using appropriate dialkoxymethanes have been described. Bicking et al.[13] studied the reaction of 2-hydroxy-4-phenyl-3-butenamide with diethoxymethane in the presence of a catalytic amount of *p*-toluenesulfonic acid. The expected *N*-ethoxymethyl-2-hydroxy-4-phenyl-3-butenamide was obtained in low yield and *N*,*N*′-methylenebis(2-hydroxy-4-phenyl-3-butenamide) was formed as the main product. A similar result was obtained by Cauliez et al.[14] who used dimethoxymethane as a co-reagent for esterification of pyroglutamic acid under acidic conditions. Instead of methyl pyroglutamate a mixture of methyl *N*-(methoxymethyl)pyroglutamate and methyl *N*,*N*′-(methylenebis)pyroglutamate was obtained in nearly equimolar ratio.

We have found that replacing the Brønsted acid with an appropriate Lewis acid makes possible the preparation of *N*-(alkoxymethyl) amides in high yields. According to our method, a secondary amide is refluxed in an excess of the appropriate dialkoxymethane in the presence of a Lewis acid (Scheme 1).[15]



Scheme 1

Representative examples of methoxy- and ethoxymethylation reactions of secondary amides and sulfonamides, including also lactams and sultams, are shown in Table 1.[16] One example of a phosphamide has been added for completeness. It is obvious that the scope of this reaction is much broader than presented in Table 1 and gives an easy access to many interesting compounds bearing *N*-alkoxymethyl groups.

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Table 1 Preparation of *N*-Alkoxymethyl Derivatives from the Appropriate N-H Substrates (Yields were not Optimized)

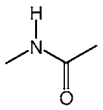
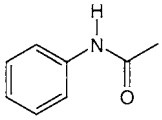
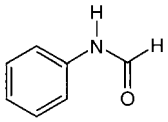
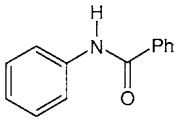
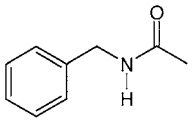
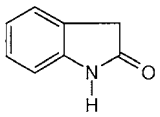
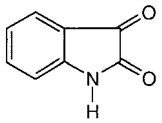
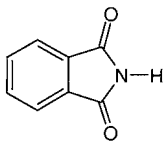
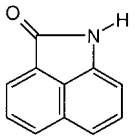
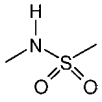
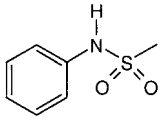
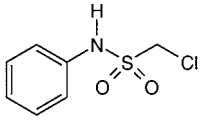
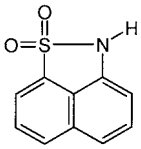
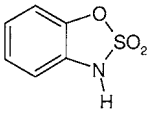
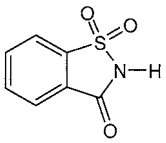
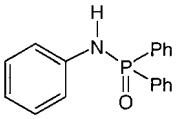
Entry	N-H substrate	$(RO)_2CH_2$	Catalyst	Time (h)	Conversion by GC/MS [%]	Isolated yield (%)
1		R = Me	$BF_3{\cdot}OEt_2$	12	95	30
2		**a**) R = Me	$BF_3{\cdot}OEt_2$	10	100	81
			$SnCl_4$	7	78	60
			$ZnCl_2$	6	<1	–
			$AlCl_3$	6	–	–
		b) R = Et	$BF_3{\cdot}OEt_2$	5	91	78
			$SnCl_4$	3.5	85	67
			$ZnCl_2$	10	<1	–
			$AlCl_3$	6	–	–
3		R = Me	$BF_3{\cdot}OEt_2$	9	88	63
4		R = Me	$BF_3{\cdot}OEt_2$	9	100	68
5		R = Me	$BF_3{\cdot}OEt_2$	27	70	56
6		R = Me	$BF_3{\cdot}OEt_2$	9.5	78	62
7		R = Me	$BF_3{\cdot}OEt_2$	8	83	69
8		**a**) R = Me	$SnCl_4$	5	94	71
		b) R = Et	$BF_3{\cdot}OEt_2$	5	70	59
			$SnCl_4$	5	88	68
		c) R = Et	$ZnCl_2$	5	50[a]	23
9		**a**) R = Me	$BF_3{\cdot}OEt_2$	5	100	79
		b) R = Et	$ZnCl_2$	5	100	61
10		R = Me	$BF_3{\cdot}OEt_2$	5.5	100	93
11		R = Me	$BF_3{\cdot}OEt_2$	5	100	87
12		R = Me	$BF_3{\cdot}OEt_2$		100	91

Table 1 Preparation of *N*-Alkoxymethyl Derivatives from the Appropriate N-H Substrates (Yields were not Optimized) (continued)

Entry	N-H substrate	$(RO)_2CH_2$	Catalyst	Time (h)	Conversion by GC/MS [%]	Isolated yield (%)
13		**a**) R = Me **b**) R = Et	$BF_3{\cdot}OEt_2$ $ZnCl_2$	5 4	100 100	90 89
14		R = Me	$BF_3{\cdot}OEt_2$	5	100	83
15		R = Me	$BF_3{\cdot}OEt_2$		100	67
16		R = Me	$BF_3{\cdot}OEt_2$	5.5	100	92

[a] For the formula of this product see Scheme 2.

To establish the optimal conditions for the alkoxymethylation reaction we have performed several experiments taking the methoxymethylation of acetanilide (entry 2 in Table 1) as a model. With $BF_3{\cdot}OEt_2$ (and other Lewis acids, too) the best results were obtained for the molar ratio between 1.2:1 and 1.3:1 Lewis acid to amide. With lower amounts of catalyst conversion factors followed the ratios catalyst to starting amide. This can be accounted for the complexation of the Lewis acid by the reaction product.

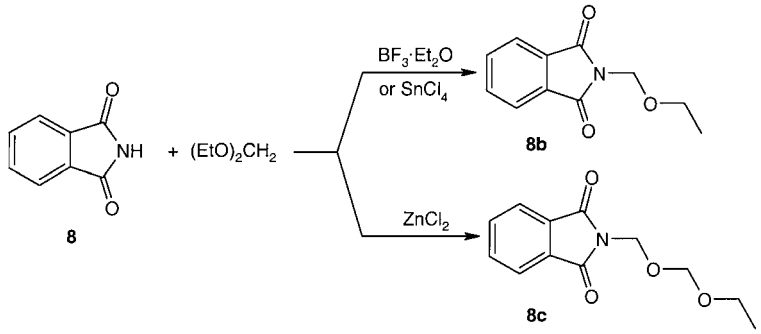
In most experiments boron trifluoride etherate was used as the catalyst because it gave the best results. However, $SnCl_4$ proved to be almost as effective. In some instances $ZnCl_2$ can work as an efficient catalyst; however for less reactive amides like acetanilide (entry 2 in Table 1) no reaction was observed. Interestingly, no reaction occurred with $AlCl_3$, possibly due to the stronger complexation of this reagent by the starting amide. Boron trifluoride etherate is a catalyst of choice also taking into account the work-up procedure. Metal chlorides like $SnCl_4$ and $ZnCl_2$ upon treatment with water alkali give voluminous precipitates, which are difficult to filter off and can adsorb significant amounts of the products. Acidic workup has to be avoided due to the susceptibility of *N*-alkoxymethyl derivatives to hydrolyze under such conditions.

Remarkably, in our case, no side products like *N*,*N*′-(methylenebis)amides have been formed, as proved by GC/MS analysis. Moreover, according to this analytical method, in most of the cases the N-H substrates were converted quantitatively. Lower yields of isolated and purified products in some instances reflect the difficulties observed during work-up of the reaction mixture. Some products, especially these with low molecular weight, like *N*-methoxymethyl-*N*-methylacetamide (entry 1), show quite good solubility in water making extraction difficult. *N*-Alkoxymethyl derivatives of amides show also a tendency to hydrolyze even under neutral or mildly basic conditions resulting in lower yields. N-Alkoxymethylated sulfonamides and phosphamides are much more stable against hydrolysis, so the isolated yields of these compounds are usually higher (entries 10–16 in Table 1). Yields presented in Table 1 were not optimized and can be significantly improved by individual modification of the work-up and purification procedures.

To prove the superiority of the Lewis acids comparing to Brønsted acids we have performed two experiments in which acetanilide and oxindole (for the formulae see entries 2 and 6 in Table 1) were refluxed with dimethoxymethane in the presence of the catalytic amounts of *p*-toluenesulfonic acid. In the case of acetanilide the expected *N*-methoxymethyl derivative was formed as the only product, but the conversion factor was never higher than 54%, independently on the amount of $(CH_3O)_2CH_2$ and *p*-TsOH used. Under the same conditions oxindole yielded two products: *N*-(methoxymethyl)oxindole and *N*,*N*′-(methylenebis)oxindole in about 2:1 ratio, together with unreacted substrate. These results show clearly that the results obtained with the Lewis acids are much better that those with *p*-toluenesulfonic acid.

Surprisingly, we found that unlike other experiments performed, the course of the reaction between 1*H*-isoindole-1,3-(2*H*)-dione (phthalimide) and diethoxymethane strongly depends on the Lewis acid employed. Hence, in the presence of boron trifluoride etherate or tin(IV) chloride the expected *N*-(ethoxymethyl)phthalimide (**8b**) forms in a good yield (Scheme 2).

However, when zinc chloride is used under the same conditions the reaction results in the formation of



Scheme 2

2-[(ethoxymethoxy)methyl]-phthalimide (**8c**) with 50% conversion (Scheme 2). The reason for such a behavior is not clear so far.

Our method seems to be limited to secondary amides, sulfonamides and phosphamides. Preliminary experiments with benzamide and *p*-toluenesulfonamide, as the representative examples of primary amides and sulfonamides, showed that it is not possible to introduce selectively a single methoxymethyl group on the nitrogen atom using dimethoxymethane/Lewis acid system. Under standard conditions[15] both compounds yielded complex product mixtures, which were not analyzed.

Acknowledgment

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(14) Cauliez, P.; Rigo, B.; Fasseur, D.; Couturier, D. *J. Heterocycl. Chem*. **1991**, *28*, 1143.
(15) **Alkoxymethylation of Secondary Amides, Sulfonamides or Phosphamides – Representative Example:** To a solution of 1-chloro-*N*-phenylmethanesulfonamide (1.03 g, 5 mmol) in dialkoxymethane (24 mL, 0.27 mol) boron trifluoride etherate **(**0.76 mL, 6 mmol) was added and the mixture was refluxed during 5 h under argon atmosphere. After cooling to r.t. the reaction mixture was treated with 3 mL of the sat. aq K_2CO_3 and the aq solution extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified by crystallization from hexane/EtOAc yielding 1.14 g (91% yield, mp 65–66 °C, lit.[17] mp 67–68 °C) of 1-chloro-*N*-(methoxymethyl)-*N*-phenylmethanesulfonamide (**12**) as white crystals.
(16) Properties of new compounds:
***N*-Benzyl-*N*-(methoxymethyl)acetamide(5).** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.24 (s, 3 H, C*H*$_3$CO), 3.28 (s, 3 H, C*H*$_3$O), 4.60 (s, 2 H, PhC*H*$_2$), 4.67 (s, 2 H, NC*H*$_2$O), 7.18–7.38 (s, 5 H, Ph). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 21.3 (*C*H$_3$CO), 48.0 (Ph*C*H$_2$), 55.3 (*C*H$_3$O), 79.5 (N*C*H$_2$O), 127.3 (Ph), 128.1 (Ph), 128.5 (Ph), 137.4 (Ph), 171.4 (CO). MS: *m*/*z* (%) = 193 (1) [M$^+$], 162 (12), 161 (71), 148 (6), 120 (31), 119 (48), 118 (30), 106 (100), 92 (8), 91 (93), 79 (10), 65 (13), 60 (14), 45 (23), 43 (48). HRMS calcd for $C_{11}H_{15}NO_2$: 193.1102. Found: 193.1113.
2-[(Ethoxymethoxy)methyl]-1*H*-isoindole-1,3-(2*H*)-dione(8c). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (t, 3 H, ^3J = 7.1 Hz, C*H*$_3$CH$_2$O), 3.56 (q, 2 H, ^3J = 7.1 Hz, CH$_3$C*H*$_2$O), 4.76 (s, 2 H, OC*H*$_2$O), 5.18 (s, 2 H, NC*H*$_2$O), 7.65–7.89 (m, 4 H, Ar*H*). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.8 (*C*H$_3$CH$_2$O), 63.6 (CH$_3$*C*H$_2$O), 64.5 (N*C*H$_2$O), 94.3 (O*C*H$_2$O), 123.5 (Ar), 131.8 (Ar), 134.2 (Ar), 167.5 (*C*O). LSIMS MS: *m*/*z* = 258 [M + Na$^+$]. Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.25; H, 5.57; N, 5.96. Found: C, 61.09; H, 5.49; N, 6.00. Mp: 61.5–62 °C (hexane/EtOAc).
2-(Methoxymethyl)-2*H*-naphtho[1,8-*cd*]isothiazole 1,1-dioxide(13a). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.52 (s, 3 H, C*H*$_3$O), 5.26 (s, 2 H, NC*H*$_2$O), 6.96–8.14 (m, 6 H, Ar*H*). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 56.7 (*C*H$_3$O), 74.4 (N*C*H$_2$O), 104.6 (Ar), 119.0 (Ar), 119.1 (Ar), 119.9 (Ar), 128.1 (Ar), 129.4 (Ar), 130.1 (Ar), 130.6 (Ar), 131.3 (Ar), 135.5 (Ar). MS: *m*/*z* (%) = 249 (23) [M$^+$], 219 (21), 218 (9), 188 (4), 154 (7), 127 (10), 77 (5), 75 (7), 74 (5), 61 (14), 45 (100), 33 (4). HRMS calcd for $C_{12}H_{11}NO_3S$: 249.0439. Found: 249.0459. Mp: 90–91.5 °C (hexane/EtOAc).
2-(Ethoxymethyl)-2*H*-naphtho[1,8-*cd*]isothiazole 1,1-dioxide(13b). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, 3 H, ^3J = 6.8 Hz, C*H*$_3$CH$_2$O), 3.75 (q, 2 H, ^3J = 6.8 Hz, CH$_3$C*H*$_2$O), 5.30 (s, 2 H, NC*H*$_2$O), 7.07–8.14 (m, 6 H, Ar*H*). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.7 (*C*H$_3$CH$_2$O), 64.6 (CH$_3$*C*H$_2$O), 72.8 (N*C*H$_2$O), 104.6 (Ar), 118.9 (Ar), 119.0 (Ar), 119.8 (Ar), 128.0 (Ar), 129.4 (Ar), 130.1 (Ar), 130.6

(Ar), 131.3 (Ar), 135.6 (Ar). MS: *m/z* (%) = 263 (47) [M^+], 233 (19), 219 (7), 218 (42), 205 (100), 172 (5), 141 (48), 140 (17), 128 (7), 127 (38), 115 (8), 114 (16), 113 (7), 77 (17), 63 (10), 59 (64), 43 (10). HRMS calcd for $C_{13}H_{13}NO_3S$: 263.0616. Found: 263.0622. Mp: 130–131 °C (hexane/EtOAc).

3-(Methoxymethyl)-3*H*-1,2,3-benzoxathiazole 2,2-dioxide(14). ^{1}H NMR (500 MHz, acetone-d_6): δ = 3.49 (s, 3 H, CH_3O), 5.28 (s, 2 H, NCH_2O), 7.13–7.34 (m, 4 H, Ar*H*). ^{13}C NMR (500 MHz, acetone-d_6): δ = 57.0 (*C*H_3O), 78.1 (N*C*H_2O), 111.9 (Ar), 112.2 (Ar), 124.0 (Ar), 126.1 (Ar), 131.4 (Ar), 142.1 (Ar). MS: *m/z* (%) = 179 (37) [$M^{+\cdot}$], 164 (2), 149 (9), 148 (14), 135 (2), 134 (3), 120 (4), 78 (4), 77 (17), 65 (4), 52 (3), 51 (8), 45 (100), 39 (3). HRMS calcd for $C_9H_9NO_3$: 179.0582. Found: 179.0575.

***N*-(Methoxymethyl)-*N*,*P*,*P*-triphenylphosphinic Amide(16).** ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.09 (s, 3 H, CH_3O), 4.62 (d, 2 H, ^3J = 13.2 Hz, NCH_2O), 6.94–7.90 (m, 15 H, Ph). ^{13}C NMR (500 MHz, DMSO-d_6): δ = 54.7 (*C*H_3O), 82.4 (d, 1 C, ^2J = 6.4 Hz, N*C*H_2O), 124.9 (Ph), 125.6 (Ph), 125.7 (Ph), 128.4 (Ph), 128.5 (Ph), 128.7 (Ph), 130.8 (Ph), 131.8 (Ph), 131.9 (Ph), 132.2 (Ph), 132.3 (Ph), 134.8 (Ph), 143.3 (Ph) (Note: number of signals is higher than the number of carbon atoms due to the ^{13}C – ^{31}P coupling in the aromatic rings). MS: *m/z* (%) = 337 (1) [$M^{+\cdot}$], 307 (1), 306 (3), 291 (1), 232 (37), 231 (100), 220 (16), 219 (37), 213 (4), 202 (15), 201 (14), 200 (8), 199 (52), 155 (19), 153 (6), 152 (13), 136 (10), 134 (13), 125 (5), 109 (9), 106 (7), 92 (12), 91 (11), 78 (9), 77 (54), 62 (12), 51 (24), 47 (8), 45 (25), 43 (24). HRMS calcd for $C_{20}H_{20}NO_2P$: 337.1231. Found: 337.1225.

(17) Danikiewicz, W.; Wojciechowski, K. *Rapid Commun. Mass Spectrom.* **1996**, *10*, 36.