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A Novel Direct Conversion of Primary Amides to Their Corresponding Methyl Esters

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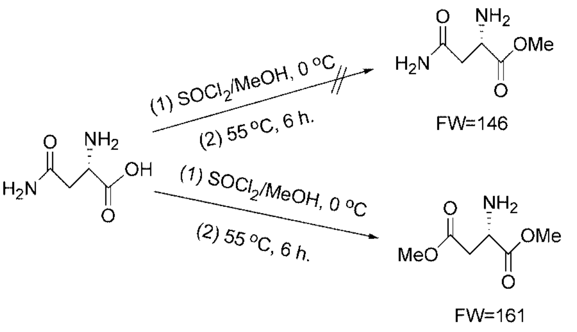
A novel method was used to directly convert aliphatic and aromatic primary amides into their corresponding methyl esters in high yields (up to 99 %) under mild reaction conditions. Possible mechanisms were studied at the B3LYP/6-31++G(d,p) level of theory. Formation of the ester proceeded through a rearrangement of the –OMe and –NH_2 groups in the RC(O)NHS(O)OMe intermediate in a H^+-catalyzed six-membered ring transition state structure.

Introduction

One of the most important tasks in chemistry is to perform functional group inter-conversions. Direct conversion of organic esters (or acids) to their corresponding amides is a common and convenient organic operation.[1–4] In contrast, the conversion of organic amides to the corresponding esters is relatively difficult. Methods to convert secondary amides into their corresponding esters with the use of $NaNO_2$ heated at reflux in 1,4-dioxane have been reported.[5–10] The conversions of primary amides to their corresponding esters were reported by using resin,[11] concentrated HCl,[12] Ti^{IV}-catalysis,[13] or Me_3SiCl.[14] Only the use of resin and Me_3SiCl in the conversion are relatively mild. Herein, we report another novel efficient solution to convert amides directly to their corresponding esters in high yields under mild reaction conditions.

Results and Discussions

The amino acid L-asparagine was readily transformed into its corresponding bis(methyl amino)ester by heating thionyl chloride with methanol at 55 °C for 6 h [Equation (1)] or at room temperature for two days. The expected amino ester was not found. The product has two singlets with equal integrated areas at δ = 3.65 and 3.69 ppm in the ^{1}H NMR spectra, respectively. The integration ratio of each of these peaks to that of the α-proton (δ =3.78 ppm) is 3:1. This demonstrated that two –COOMe groups were present in the molecule. Mass spectra (EIMS) exhibited a molecular weight of 161 for the product, which confirms bis(ester) formation.[15] The methanol solution of $SOCl_2$ can catalyze the conversions of seven aromatic primary amides (Entries 1–10) and two aliphatic primary amides (Entries 11, 12) into their corresponding methyl esters under the same reaction conditions (Table 1). The structures of methyl esters were only identified by ^{1}H NMR and ^{13}C NMR spectroscopic analysis because all of the esters are known products [Equation (1)].



(1)

HCl that is formed from $SOCl_2$ and methanol may directly catalyze the conversion as shown in Figure 1.

However, 2 mol of dried HCl in methanol cannot catalyze the conversion of 1 mol of L-asparagine to the corresponding methyl ester in reasonable yields in tightened glassware in two days (< 5% at room temperature) in our experiments. In contrast to this result, L-asparagine could be transformed into the methyl esters by using $SOCl_2$ and methanol at room temperature.[16] HCl may be involved in the transition states. However, this direct conversion mechanism cannot explain why the conversion of L-asparagine to bis(ester) can take place at room temperature in our studies. Obviously, the reaction in our experiments must involve

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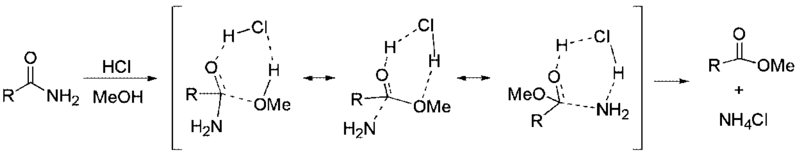
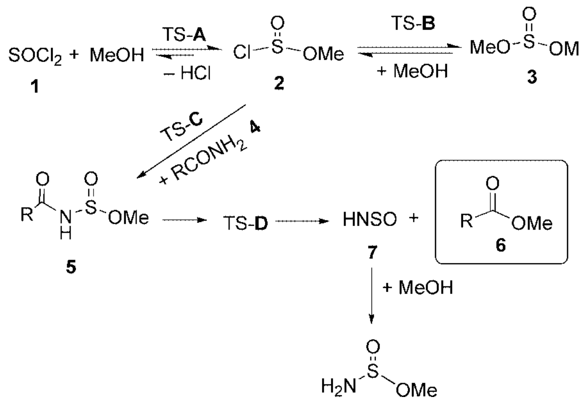


Figure 1. HCl direct catalysis mechanism of amide to its methyl ester.

Table 1. The conversions of primary amides to the corresponding methyl esters in methanol.[a]

Entry	R	Amide:$SOCl_2$ [mol ratio]	T [°C]	Yield [%][b]
1	Ph-	1:1.1	20	87
2	Ph-	1:1.1	55	86
3	Ph-	1:2.0	55	92
4	Ph-	1:3.0	55	93
5	3-F-C_6H_4-	1:1.1	55	93
6	(*E*)-PhCH=CH-	1:1.1	55	83
7	4-CH_3-C_6H_4-	1:1.1	55	99
8	3-CH_3-C_6H_4-	1:1.1	55	96
9	4-OH-C_6H_4-	1:1.1	55	90
10	2-NH_2-C_6H_4-	1:1.1	55	75
11	(1-naphthyl)-CH_2-	1:1.1	55	92
12	Me	1:1.1	55	70[c]

[a] See ref.[16] in Supporting Information section for reaction procedure. [b] Isolated yields. [c] The boiling point of methyl acetate is very low. Methyl acetate that was formed was converted to sodium acetate by using NaOH in methanol at room temperature. The yield was then computed on the basis of the dried quantity of NaOAc obtained.



Scheme 1.

some other complex mechanism even if the HCl catalysis mechanism exists.

The proposed mechanism is shown in Scheme 1. Entire molecules including the S and Cl atoms of $SOCl_2$ are involved in the transition state (TS) structures. This treatment is the same as our previous reports.[17–19] The mechanism was investigated by using DFT theory at the B3LYP/6-31++G(d,p) level in the gas phase. Their energy magnitudes in methanol were corrected with the use of the PCM model by computing their single point energy by using the geometries obtained in the gas phase.[20–26] The lowest energy conformers of substrate complexes (precursors of TS) were used for barrier computations. The electronic energy data were used in the barrier computations in this method. The detailed energetics and structures and other information involved in this mechanism are provided in the Supporting Information.

The rapid formation of **2** from **1** occurs via TS-**A** over a 20.7 kcal/mol energy barrier in methanol (Figure 2). Reversible reaction to **1** is more difficult because this predicted barrier is 23.6 kcal/mol. Compound **2** could either react with another molecule of methanol to give **3** or react with amide **4** to produce intermediate **5**.[27] The barrier from **2** to **3** is 18.1 kcal/mol, whereas the energy barrier for the reverse reaction (from **3** to **2**) is only 18.8 kcal/mol. Thus, equilibrium exists between **2** and **3**. When R = Me, the barrier predicted from **2** to intermediate **5** proceeds through TS-**C** with a magnitude of 19.7 kcal/mol, only 1.6 kcal/mol higher than the barrier to TS-**B** (Figure 2). Therefore, if **5** were converted into methyl ester **6**, the equilibrium between **2** and **3** would supply **2** for conversion to **5**. Finally, the conversion of **5** to **6** is the key TS step. This step proceeds through TS-**D**.

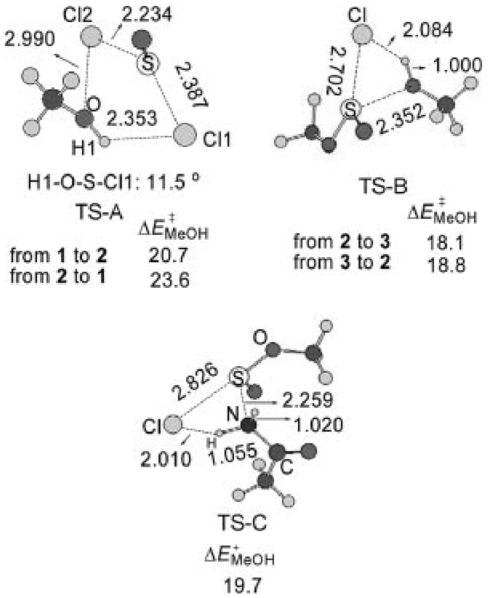
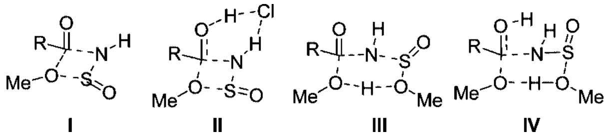


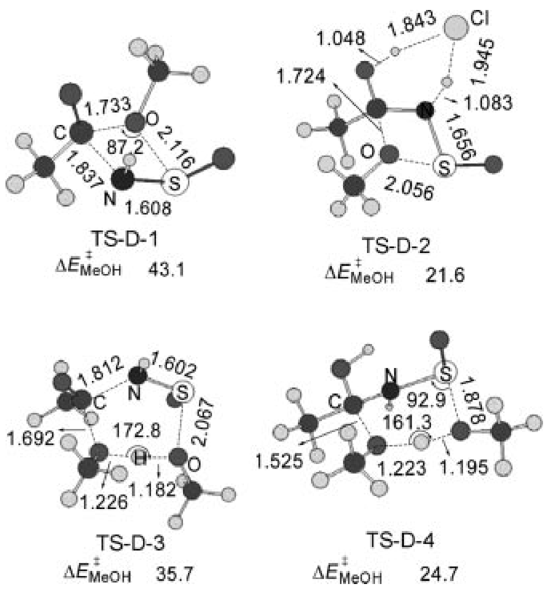
Figure 2. Transition state structures of TS-**A** to TS-**C** and their TS barriers in methanol (energies in kcal/mol).

Four- and six-membered ring TS geometries, with or without H^+ or HCl catalysis, were investigated. TS structures **I**, **II**, **III**, and **IV** were considered reasonable for structure studies of TS-**D** (Figure 3). The structures obtained for TS-**D** with the lowest computed energies for each of the TS types (**I**, **II**, **III**, and **IV**), and their barriers, are illustrated in Figure 4.



I **II** **III** **IV**

Figure 3. Four types of transition states involved in TS-**D** geometries.



TS-D-1 $\Delta E^{\ddagger}_{\mathrm{MeOH}}$ 43.1

TS-D-2 $\Delta E^{\ddagger}_{\mathrm{MeOH}}$ 21.6

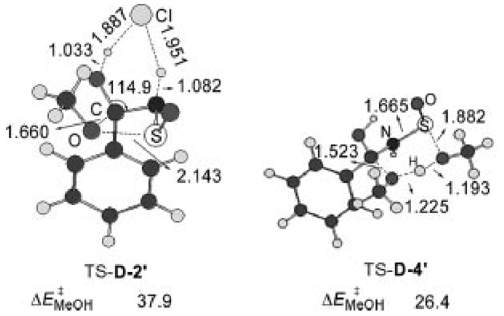
TS-D-3 $\Delta E^{\ddagger}_{\mathrm{MeOH}}$ 35.7

TS-D-4 $\Delta E^{\ddagger}_{\mathrm{MeOH}}$ 24.7

Figure 4. Four TS-**D** structures and their predicted barriers in conversions of acetamide to their corresponding methyl esters in MeOH (energies in kcal/mol).

DFT calculations indicate that the lowest barriers found without acid catalysis was 43.1 kcal/mol in methanol for conversions proceeding through four-membered ring TSs (TS-**D-1**). This is almost impossible in reactions. The HCl-catalyzed four-membered TS structure TS-**D-2** has an activation barrier of only 21.6 kcal/mol in methanol. In type **III**, six-membered ring TS structure TS-**D-3**, a second molecule of methanol was involved in the TS. The lowest energy barrier, 35.7 kcal/mol in MeOH, was found. The barrier to six-membered ring TS-**D-4** of acetamide is 24.7 kcal/mol in methanol. This value in methanol is 3.1 kcal/mol higher in energy than that of HCl-catalyzed four-membered ring TS-**D-2**. TS-**D-2** and TS-**D-4** are both possible TS structures, and TS-**D-2** looks favorable.

The H^+-catalyzed four- and six-membered ring TSs, TS-**D-2**′ and TS-**D-4**′, in the reaction of benzamide with thionyl chloride in methanol were also investigated. The TSs and their barriers are illustrated in Figure 5. The barrier in methanol in four-membered ring **TS-D-2**′ increased sharply from 21.6 to 37.9 kcal/mol when acetamide was replaced by benzamide in the TS computations. In contrast, the barrier in the six-membered ring only increased from 24.7 to 26.4 kcal/mol. Because the reactions take place at 50 °C, the possible TS should theoretically be an H^+-catalyzed six-membered ring structure in the reaction of amide with thionyl chloride in methanol.



TS-**D-2'** $\Delta E^{\ddagger}_{\mathrm{MeOH}}$ 37.9

TS-**D-4'** $\Delta E^{\ddagger}_{\mathrm{MeOH}}$ 26.4

Figure 5. The TSs and their barriers in methanol in the reaction of benzamide with thionyl chloride in methanol (energies in kcal/mol).

More experiments were carried out to test which TS geometry is possible. Reactions in THF showed that the presence of two or more mol of methanol per one mol of acetamide and benzamide is necessary for conversion of the amides to their esters.[28] The effects of alcohol structure and quantity on yields of benzamide conversion were studied (Table 2). The low isopropyl ester yield obtained (21%; Table 2, Entry 9) was expected because of the steric factors of the isopropyl group. The yield is lower than that of methyl ester by 44% (Table 2, Entry 7). Overall, an H^+-catalyzed six-membered ring TS, TS-**D-4** (type **IV**), is the possible TS geometry.

Table 2. Effect of the ratio of benzamide/$SOCl_2$/ROH on the reaction yields in dried THF solution.[29]

Entry	*T* [°C]	Ratio of benzamide/$SOCl_2$/ROH	Yield [%][a]	Recovered benzamide [%]
1	–5	1:1.1:1.1 (R = Me)	0	98
2	–5	1:1.1:2 (R = Me)	tiny	99
3	–5	1:1.1:4–6 (R = Me)	5–10	85–93
4	–5	1:1.1:8 (R = Me)	21	76
5	–5	1:1.1:10 (R = Me)	22	76
6	–5	1:1.1:14 (R = Me)	42	53
7	55	1:1.1:25 (R = Me)	65	32
8	55	1:1.1:25 (R = Et)	56	40
9	55	1:1.1:25 (R = *i*Pr)	21	73

[a] Isolated yields.

In summary, a novel direct conversion of primary amides to their corresponding methyl esters has been achieved in high yields under mild reaction conditions by using thionyl chloride and methanol heated at 55 °C. Thus, the amide group could be conveniently used as an acid or ester synthon. Aside from the HCl direct catalysis mechanism, the likely TS geometries for these reactions have been predicted by using the B3LYP/6-31++G(d,p) level of theory. The possible TS geometry in the conversions involves the H^+-catalyzed rearrangement of –OMe and –NH_2 groups of the RC(O)NHS(O)OMe intermediate via a six-membered ring TS structure in which a second molecule of methanol is needed. Secondary and tertiary amides cannot undergo this conversion under these reaction conditions. Different chemoselectivities will be discussed in subsequent studies.

Experimental Section

NMR spectra were recorded with a Bruker-AV-400 instrument with the use of $CDCl_3$ as the solvent, unless another solvent is specifically stated. Chemicals and silica gel (200–400 mesh) were bought and used as received. Autospec was used for MS determination.

All compounds involved in the experiments are known. Thus, only ^{1}H and ^{13}C NMR spectra were determined. The general experimental procedure is summarized in the Supporting Information. The NMR spectroscopic data of all compounds involved in this paper are listed below.

PhCOOMe (1): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, J = 7.6 Hz, 2 H), 7.57 (t, J = 7.2 Hz, 1 H), 7.46 (t, J = 7.6 Hz, 2 H), 3.93 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 132.7, 129.9, 129.3, 128.2, 51.8 ppm.

3-F-PhCOOMe (2): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (s, 1 H), 7.86 (d, J = 8.0 Hz, 1 H), 7.47 (dd, J = 8.0 Hz, 0.8 Hz, 1 H), 7.32 (t, J = 8.0 Hz, 1 H), 3.88 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 134.4, 132.8, 132.7, 129.5, 127.5, 52.2 ppm.

(*E*)-PhCH=CHCOOMe (3): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, J = 16.0 Hz, 1 H), 7.52 (d, J = 3.6 Hz, 2 H), 7.39 (s, 3 H), 6.44 (d, J = 16.0 Hz, 1 H), 3.81 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 144.8, 134.3, 130.2, 128.8, 128.0, 117.7, 51.7 ppm.

4-CH_3-PhCOOMe (4): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.0 Hz, 2 H), 7.22 (d, J = 8.0 Hz, 2 H), 3.89 (s, 3 H), 2.39 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 143.2, 129.3, 128.8, 127.2, 51.6, 21.3 ppm.

3-CH_3-PhCOOMe (5): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (m, 2 H), 7.35 (m, 2 H), 3.90 (s, 3 H), 2.40 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 137.9, 133.4, 129.9, 128.0, 126.5, 51.7, 20.9 ppm.

4-HO-PhCOOMe (6): ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 9.21 (s, 1 H), 7.87 (d, J = 8.4 Hz, 2 H), 6.91 (d, J = 8.8 Hz, 2 H), 3.81 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 166.9, 132.3, 122.3, 115.9, 51.8 ppm.

2-NH_2-PhCOOMe (7): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (m, 1 H), 7.25 (m, 1 H), 6.64 (t, J = 8.0 Hz, 2 H), 3.86 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 150.3, 133.9, 131.1, 116.6, 116.2, 110.7, 51.38 ppm.

1-Naph-CH_2COOMe (8): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.0 Hz, 1 H), 7.88 (d, J = 8.0 Hz, 1 H), 7.81 (d, J = 7.6 Hz, 1 H), 7.58–7.43 (m, 4 H), 4.09 (s, 2 H), 3.70 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 133.8, 132.0, 130.5, 128.7, 128.0, 127.9, 126.4, 125.7, 125.4, 123.7, 52.1, 39.0 ppm.

$PhCOOCH_2CH_3$ (9): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, J = 7.2 Hz, 2 H), 7.55 (t, J = 7.6 Hz, 1 H), 7.44 (t, J = 7.6 Hz, 2 H), 4.38 (q, J = 5.6 Hz, 2 H), 1.39 (t, J = 5.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 132.8, 130.5, 129.5, 128.3, 60.9, 14.3 ppm.

$PhCOOCH(CH_3)_2$ (10): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, J = 8.0 Hz, 2 H), 7.52 (t, J = 7.6 Hz, 1 H), 7.41 (t, J = 8.0 Hz, 2 H), 5.25 (m, 1 H), 1.36 (d, J = 6.0 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 132.5, 130.7, 129.3, 128.1, 68.2, 21.8 ppm.

$MeOOCCH_2CH(NH_2)COOMe$ (11): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.78 (m, 1 H), 3.69 (s, 3 H), 3.65 (s, 3 H), 2.76 (dd, J = 5.0 Hz, 16.5 Hz, 1 H), 2.66 (dd, J = 7.0 Hz, 17.2 Hz, 1 H) ppm. MS: m/z = 161 $[M]^+$.

Supporting Information (see footnote on the first page of this article): Experimental procedure, energy data and coordinates for all TSs, IRC plots, and ^{1}H NMR and ^{13}C NMR spectroscopic data.

Acknowledgments

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[15] This compound is known and only ^{1}H NMR and mass spectra were recorded. The NMR spectroscopic data was compared with the known data. Details of the reaction procedure are summarized in ref.[11] in the Supporting Information.

[16] See Supporting Information for reaction details.

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[28] Experiments were performed to define the smallest mol ratio of MeOH/acetamide where **6** would still be formed. However, because the methyl acetate formed has a low boiling point, further studies to determine the yields were not performed.

[29] See the Supporting Information for reaction details.

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