Reaction Mechanisms

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Mechanism of Methyl Esterification of Carboxylic Acids by Trimethylsilyldiazomethane**

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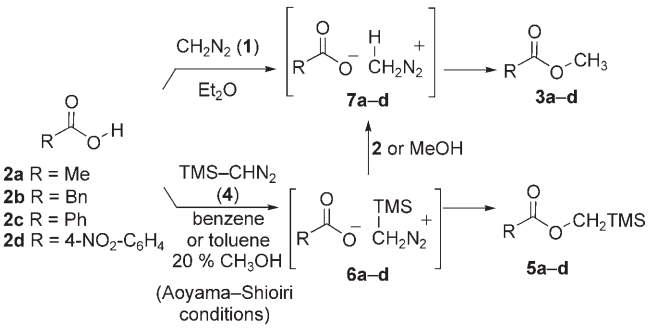
Despite being toxic, flammable, photosensitive, thermally unstable, and shock sensitive, diazomethane (CH_2N_2, **1**) has had extensive application in synthesis, especially for the *O*-methylation (esterification) of carboxylic acids (**2**→**3**), Scheme 1.



Scheme 1. Methyl esterification of carboxylic acids (**2**) by diazomethane (**1**) and by trimethylsilyl diazomethane (**4**), with Aoyama–Shioiri mechanism for **4**→**3**+**5**. Bn = benzyl.

In 1968 Seyferth et al. reported[1] that the trimethylsilyl (TMS) derivative of diazomethane (TMS−CHN_2, **4**),[2,3] described by Lappert et al.[2a] reacts with acetic acid (**2a**) in dry benzene to generate TMS-methyl acetate (**5a**), Scheme 1. This reaction was proposed to arise from the protonation of **4** by **2a** and then nucleophilic substitution of N_2 by acetate in the resulting TMS-substituted methyl diazonium intermediate (**6a**→**5a**).[1,4] However, AcOTMS and methyl acetate (**3a**) were also generated in 40–60% yield. Seyferth et al. suggested that the intermolecular protodesilylation of intermediate **6a** by the acetic acid generates a methyl diazonium intermediate [AcO][CH_3N_2] (**7a**), thus yielding **3a**.[1] In 1981 Aoyama, Shioiri, and co-workers reported that a simple modification of the conditions reported by Seyferth et al. involving the addition of methanol as a cosolvent (20% v/v, 4.94 M), increased the yields of methyl esters **3** to near quantitative (90–99%).[5a,b] Unlike **1**, which is a gas (b.p. −23 °C) and requires prior generation from toxic and irritant *N*-methyl *N*-nitroso species, TMS−CHN_2 (**4**) is a stable liquid (b.p. 96 °C)[1] that is easily handled and is commercially available.

Over the last 26 years, the conditions reported by Aoyama, Shioiri, and co-workers (**4**, 5 M CH_3OH in toluene or benzene)[5a] have been widely adopted as a safe and convenient alternative to the use of **1** for methyl esterification,[3] especially by analytical chemists for acid derivatization prior to chromatographic analysis.[6] Although it is known that methanol is not the methylating agent,[7] the mechanism of the reaction has not been investigated in any detail.[3b,5a] Herein we demonstrate, by way of isotopic labeling, that the methyl esterification of carboxylic acids by **4**/CH_3OH proceeds through the in situ methanolytic liberation of diazomethane (**1**).

The key feature of the conditions reported by Aoyama, Shioiri, and co-workers[5a] is the high-yielding and rapid (< 5 min) generation of methyl esters **3**, rather than TMS-methyl esters **5**, through the presence of a large excess (> 50 equiv) of methanol in benzene,[5] or toluene.[3,6] ^{1}H NMR analysis demonstrates that, in the absence of added acid, **4** does not observably react with CD_3OD (5 M) in [D_8]toluene over a period of hours, although very slow H/D exchange is detected over longer periods. To explore the key role of methanol, we have focused on the reaction of phenyl acetic acid (**2b**) with **4**, and correlated the partitioning between methyl ester **3b** and TMS-methyl ester **5b** as a function of methanol concentration and isotope effect (CL_3OL; L = H/D). To ensure that the partitioning (**3b**/**5b**) was not compromised by competing or subsequent processes, we conducted the methyl esterification of benzoic acid (**2c**) in the presence of labeled esters of phenyl acetic acid (Scheme 2; a) $^2H_3$-**3b**, b) $^2H_2$-**5b**). Experiments performed with phenyl acetic acid (**2b**) and labeled esters of benzoic acid ($^2H_3$-**3c** and $^2H_2$-**5c**) proceeded analogously. The complete lack of participation of the co-reacted esters in all of these experiments confirms that: 1) the labeled products **3** and **5** are stable under the reaction conditions, 2) the product ratios **3**/**5** are kinetic and not thermodynamic, and 3) the methyl esters **3** are not generated in situ from **5** by TMS cleavage.

Analysis of the reaction of phenyl acetic acid (**2b**) under the conditions reported by Aoyama, Shioiri, and co-workers (5 M CH_3OH)[5a] in terms of attack of **6b** by methanol (k_2, Figure 1) against nucleophilic attack of phenylacetate to

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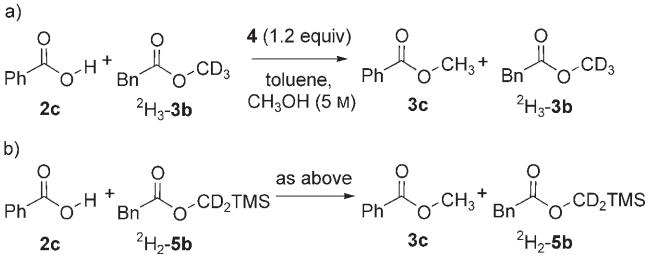
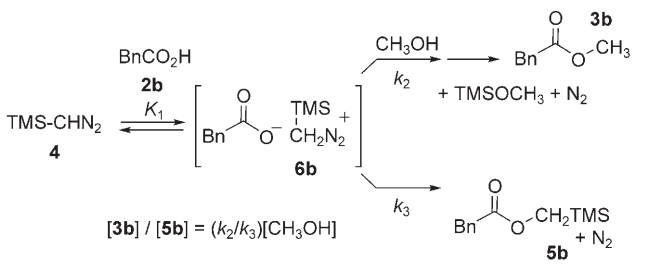


Scheme 2. Control experiments conducted with benzoic acid (**2c**) and ^{2}H-labeled phenyl acetic esters **3b** and **5b**. Experiments, in which the Bn and Ph were reversed, proceeded analogously.



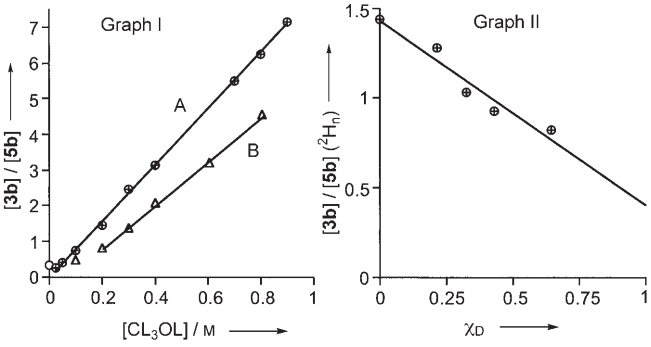


Figure 1. Kinetics of the reaction of phenyl acetic acid (**2b**) with TMS-diazomethane (**4**. Graph I: line A: **2b** (0.05 M), **4** (0.06 M) in toluene at RT; line B: as A except CD_3OD employed. Graph II: proton-inventory of [**3b**/**5b**] at $[CL_3OL] = 0.2$ M against χ_D, the mole fraction of exchangeable deuterium across the system {**2b** + **4** + CL_3OL}.

generate **5b** (k_3, Figure 1), suggests that the fate of **6b** will be determined by the absolute methanol concentration [CH_3OH], the steric bulk/nucleophilicity of the carboxylate ion (k_3), and the pK_a of **2b** (k_2 and K_1, see below). With the additional information provided by Scheme 2 regarding the inertness of the products under the reaction conditions, the analysis predicts that [**3b**]/[**5b**] = {(k_2/k_3) × [CH_3OH]}, independent of the concentration of either **2** or **4**, and that [**3b**]/[**5b**] will be constant when CH_3OH is in large excess.

The predicted first-order dependency of [**3b**]/[**5b**] (*y* axis, Figure 1) on [CH_3OH] (*x* axis) was explored at methanol concentrations below that of the standard synthetic procedure (5 M), so that the [**3b**]/[**5b**] ratios could be accurately measured (Figure 1, Graph I, line A). Curvature in the correlation is evident at very low methanol concentration, such that when [CH_3OH] = 0, thus, under "Seyferth conditions",[1] a non-zero value (0.31) of [**3b**]/[**5b**] is observed. This effect probably arises from two factors: 1) at low methanol concentrations, intermediate **6b** will be a non-dissociated ion pair, and 2) the background reaction of **6b** with acid **2b** (Seyferth-type mechanism,[1] Scheme 1) noticeably contributes. At higher methanol concentrations, the line of best-fit yields $k_2/k_3 = 7.9$ dm^{3}mol^{-1} as the partitioning of **6b** towards methanol (→**3b**) and the ion-pair reaction (→**5b**). Consistent with the analysis of the scheme in Figure 1, the [**3b**/**5b**] ratio was independent of $[\mathbf{2b}]_0$ (0.05–0.2 M).

When the reaction of phenyl acetic acid (**2b**) was carried out in the presence of *t*BuOH (1.6 M), the same ratio of **3b**/**5b** resulted as at $[CH_3OH] = 0$, and thus *t*BuOH does not interact productively with **6b**. In the presence of *t*BuOD (1.6 M), the TMS-methyl ester [^2H_n]-**5b** is obtained with a high proportion of the $^2H_2$ isotopologue (75%), thus demonstrating that the protonation of **4** by [$^2H_1$]-**2b**, to generate [$^2H_1$]-**6b**, is reversible (K_1), with the *t*BuOD acting as a nonparticipative ^{2}H reservoir. Analysis of the dependency of methyl [^2H_n]-**3b** against TMS-methyl [^2H_n]-**5b** esterification on the concentration of CD_3OD also yielded a simple correlation, Figure 1, line B. Curvature is again observed at low [CD_3OD] such that line B meets the *y* axis at the same point as line A (CH_3OH). A key point that emerges is that in the linear regime (> 0.2 M CD_3OD), the gradient of line B ($k_2/k_3 = 6.2$ dm^{3}mol^{-1}) is less than that of line A, which indicates that there is a small and normal kinetic isotope effect (KIE; k_H/k_D) for the reaction of **6b** with CL_3OL. The differential gradients of A and B suggest the KIE ($k_{2(H)}/k_{2(D)}$) that arises from the capture of **6b** by methanol to be 1.8 ± 0.5, in the concentration range 0.2–0.75 M. The small magnitude of the KIE suggests an early transition state that arises from an exothermic reaction of **6b** with the methanol. A second set of reactions were conducted with CH_3OH/CD_3OD mixtures (Figure 1, Graph II). The approximately linear correlation of [[^2H_n]-**3b**/[^2H_n]-**5b**] (*y* axis) against χ_D, the mole fraction of exchangeable ^{2}H (*x* axis), suggests that partitioning of **6b** involves the transfer of a single proton from the methanol (k_3).[8]

The isotope ratios in esters [^2H_n]-**3b** and [^2H_n]-**5b** act as proxies for the ratios in the corresponding methyl diazonium [^2H_n]-**7b** and TMS-methyl diazonium [^2H_n]-**6b** intermediates. When reactions are conducted in CD_3OD (0.2–0.8 M; χ_D = 0.65–0.88), comparison of the isotope distributions in [^2H_n]-**5b** with statistical distributions based on χ_D (Figure 2, Graph III) shows that **6b** undergoes around 90% equilibration with the CL_3OL medium (**6b**→[^2H_n]-**6b**) before partitioning to [^2H_n]-**3b** and [^2H_n]-**5b**.

However, analysis of the methyl ester [^2H_n]-**3b** reveals very different ^{2}H distributions to those predicted by the Aoyama–Shioiri–Seyferth mechanism, Scheme 1. For example, at 0.75 M concentration of CD_3OD (Figure 2, Graph IV) the apparent isotope effect for the conversion of [^2H_n]-**6b** into [^2H_n]-**3b** is 7.5 ± 0.5 (open circles). Since the isotope effect for methanolysis of **6b** ($k_{2(H)}/k_{2(D)}$) is only 1.8 ± 0.5 under these conditions (Figure 2, Graph IV, closed circles), this conclusively proves that the reaction of methanol with TMS-methyl diazonium **6b** does not lead directly to methyl ester **3b**. Instead, a process of ^{2}H/^{1}H selection (with a net KIE of 7.5 ± 0.5) must occur after C–Si bond cleavage, but prior to generation of [^2H_n]-**3b**. A likely candidate for such equilibration is diazomethane (**1**). Indeed, reaction of ethanol-free **1**

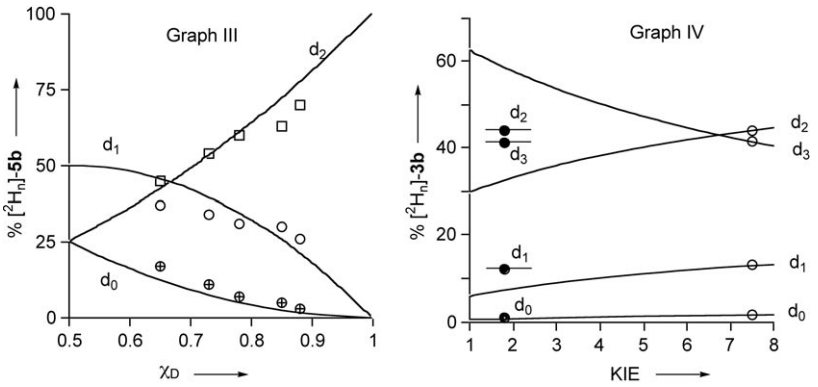


Figure 2. Graph III: d_0-, d_1-, and d_2-isotope distributions for [^2H_n]-**5b** as a function of χ_D; observed data: squares d_2, circles d_1, crossed circles d_0; solid lines: statistical distributions. Graph IV: d_0-, d_1-, d_2-, and d_3-isotope distributions for [^2H_n]-**3b** at $[CD_3OD]_0 = 0.75$ M ($\chi_D = 0.88$) as a function of KIE; solid lines: based on isotope distribution in [^2H_n]-**6b** (as determined from [^2H_n]-**5b**); observed data: closed circles, using $k_{2(H)}/k_{2(D)} = 1.8 \pm 0.5$, open circles using k_H/k_D (net) $= 7.5 \pm 0.5$.

with **2b** in toluene/CD_3OD (5 M; $\chi_D = 0.98$) gave [^2H_n]-**3b** in which 48% was the [$^2H_3$]-isotopologue. Equilibration of **1** with the CL_3OL medium, via methyl diazonium **7b**, is thus slightly greater than the rate of generation of **3b**, thus facilitating partial generation of [$^2H_2$]-**1**.[9] Under identical conditions ($\chi_D = 0.98$), TMS–CHN_2 (**4**) also gave [$^2H_3$]-**3b** as 48% of the [$^2H_3$]-isotopologue. On using *O*-[D_1]-phenyl acetic acid ([$^2H_1$]-**2b**; 5 M MeOD; $\chi_D = 0.99$), we isolated [$^2H_3$]-**3b** in 92% yield with 96% methyl per-deuteration.

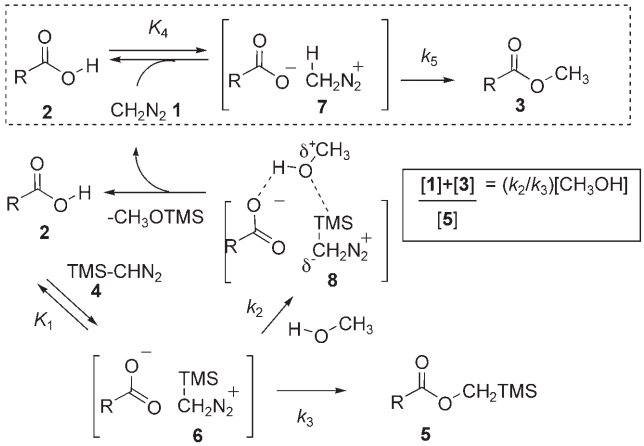
In general, C-protodesilylation reactions proceed through either a pre- or post-protonation mechanism. Synchronous protonation (as in Scheme 1) is rare. In the pre-protonation mechanism, an sp^2-hybridized carbon atom, α or γ to the silicon atom, is protonated to generate a β-carbocation from which R_3Si is eliminated. Thus allyl, vinyl, and cyclopropylmethylene silanes readily undergo cleavage,[10] whereas alkyl silanes are inert. The cationic moiety of intermediate **6** bears only sp^3-hybridized carbon atoms, and thus lacks an appropriate orbital for C-protonation. The post-protonation mechanism involves the nucleophilic displacement of the silyl group[11] to generate a carbanion.[12] The TMS group in intermediate **6** bears diazomethane (**1**) as a potential nucleofuge and the carboxylate counterion can assist the nucleophilic attack of methanol at the silicon center[13] by deprotonation of the developing methoxonium group (**8**, Scheme 3). The carboxylic acid **2** thus acts as a catalyst, first as a general acid (K_1), then as a general base, (k_2), for the methanolysis of **4** to generate free diazomethane (**1**).[14] The methyl ester is generated in a subsequent, but standard, reaction of the carboxylic acid (**2**) with the diazomethane **1** (K_4, k_5).

The competing generation of TMS-methyl esters **5** can be a problem when making derivatives for chromatographic analysis,[6a,d] and is exacerbated by weak carboxylic acids, which generate a more nucleophilic carboxylate anion (k_3). The mechanism outlined in Scheme 3 shows that the carboxylic acid plays two separate roles in the reaction: 1) it catalyses the generation of **1** from **4** and 2) acts as a reactant to generate the methyl ester **3**. The **3**/**5** ratio obtained with one acid can therefore be influenced by the presence of another.

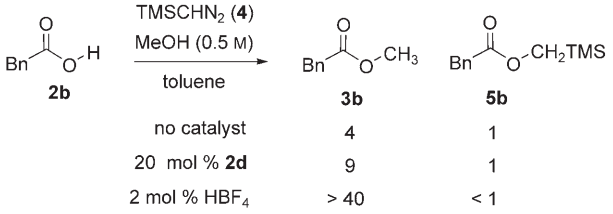
Reaction of phenyl acetic acid (**2b**) with **4** in toluene/MeOH (0.5 M) in the presence of the stronger *para*-nitrobenzoic acid (**2d**, 0–20 mol%) resulted in a moderate linear increase in the ratio of **3b**/**5b** (from 4/1 to 9/1; Scheme 4), albeit accompanied by the *para*-nitrobenzoate esters **3d** and **5d**.

The much stronger acid HBF_4, known to induce the methylation of alcohols by both **1**[15] and **4**,[5d] proved much more efficient. Using just 2 mol% led to essentially instantaneous esterification of **2b** and to a profound increase in the selectivity for **3b** over **5b** (>40/1). Since the HBF_4 also catalyses the etherification of the methanol,[5d,15] an excess of **4** (2.5 equiv) is required to attain complete conversion of **2b**.

In conclusion, we have demonstrated that methyl esterification of carboxylic acids with TMS-diazomethane (**4**) under the Aoyama–



Scheme 3. A modified mechanism for the methyl esterification of carboxylic acids (**2**) by **4** in toluene/MeOH.



Scheme 4. Acid-catalyzed methanolysis of **4**, which facilitates higher selectivity in the esterification of **2b** (0.05 M).

Shioiri conditions,[5] a procedure widely adopted for its safety,[3,6] proceeds by a methanolytic protodesilylation of **4** to generate the free diazomethane (**1**). Two key features of the mechanism, outlined in Scheme 3, are that the protonation of both **4** and **1** are reversible (K_1 and K_4), and that the apparent partitioning of intermediate **6** can be perturbed by co-reaction with strong acids. This information has facilitated

the development of an HBF_4-catalysed method to substantially improve the selectivity for **3** over **5**. It also reveals how CD_3 esters can be generated in useful isotopic purity (> 96% methyl per-deuteration) using [$^2H_2$]-**1**, generated in situ from **4** and MeOD, as a much safer alternative to the use of preformed **1**.[6c,16]

Experimental Section

[$^2H_3$]-**3b**: All manipulations prior to work-up were conducted using MeOD-washed glassware. A solution of **4** in Et_2O (0.50 mL, 1.0 mmol) was stirred in a mixture of toluene (20.86 mL) and MeOD (4.17 mL) under nitrogen for 5 h. The acid *O*-[$^2H_1$]-**2b** (136 mg, 1.0 mmol) dissolved in MeOD (1.0 mL) was then added to give a yellow solution. After stirring for 30 min at ambient temperature, during which period there was nitrogen evolution and a gradual dissipation of color, the reaction mixture was diluted with ether (20 mL) and AcOH (10% aq, 10 mL) added. The aqueous phase was extracted three times with diethyl ether and the combined organic extractions washed with saturated aq Na_2CO_3 solution, dried ($MgSO_4$) and evaporated to give [$^2H_3$]-**3b** as a colorless solid (138 mg, 92%). ^1H NMR analysis indicated the ratio of [^2H_n]-**3b**/[^2H_n]-**5b** of greater than 50/1 and that [^2H_n]-**3b** comprised 90.6% [$^2H_3$]-**3b**, 7.9% [$^2H_2$]-**3b**, 1.3% [$^2H_1$]-**3b**, and < 0.2% **3b**.

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