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MANNICH-TYPE REACTION OF *N*,*O*-ACETALS WITH KETONES MEDIATED BY A COMBINATION OF $TiCl_4$ AND $PhSiCl_3$[†]

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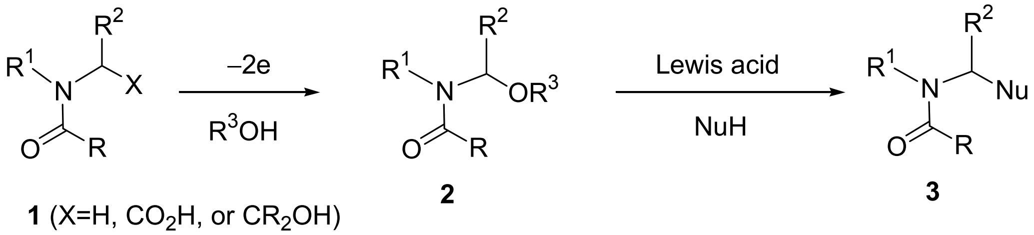
Abstract – A combination of $TiCl_4$ and $PhSiCl_3$ efficiently conducts the Mannich-type reaction of *N*,*O*-acetals with ketones to afford α-substituted cyclic amine derivatives in good yields. This method was applicable to preparation of azabicyclo compounds by the intramolecular Mannich-type reaction.

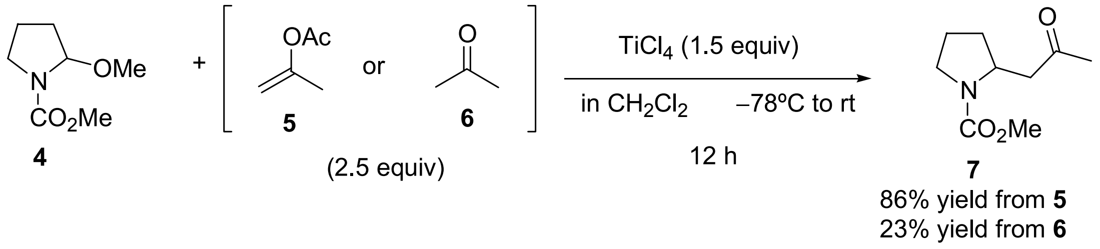
INTRODUCTION

Lewis acid mediated Mannich-type reaction between *N*,*O*-acetals **2** prepared by electrochemical oxidation[1] of amine derivatives **1** and carbon nucleophiles (NuH) is one of powerful methods for syntheses of α-substituted amine derivatives **3** (Eq. 1).[2,3] We have already reported that some active methylene compounds such as malonates, acetoacetates, and some modified ketones such as enol ethers and enol esters reacted well with **2** as the carbon nucleophiles to form the corresponding α-substituted amine derivatives with high yields.[4,5] However, similar reactions between **2** and unmodified ketones did not proceed with good yields. For example, as shown in Eq. 2, although the reaction of *N*,*O*-acetal **4** with isopropenyl acetate (**5**) gave the desired α-acetonylated product **7** in 86% yield, the yield of **7** from acetone (**6**) was only 23%. We report herein one of the most powerful protocols for $TiCl_4$-mediated Mannich-type reaction of **2** with unmodified ketones promoted by co-existing $PhSiCl_3$.



(1)

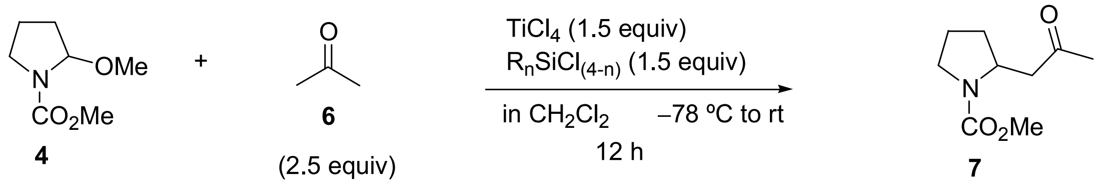
[†] Dedicated to Professor Dr. Albert Eschenmoser, ETH Zürich, on his 85th birthday.



(2)

RESULTS AND DISCUSSION

Since one reason of the low yield of **7** from **6** seemed to be that **6** hardly enolized under the reaction conditions, we tested combinations of $TiCl_4$ and some chlorosilanes[6,7] which might accelerate enolization of **6** (Eq. 3). These results are summarized in Table 1. Although in the case of using mono- and di-chlorosilanes the yields of **7** were low (entries 1 and 2), using trichlorosilanes and tetrachlorosilane improved the yields (entries 3-6).



(3)

Table 1. Effect of some chlorosilanes on the reaction of **4** with **6**.

Entry	$R_nSiCl_{(4-n)}$	Yield (%) of **7**
1	Me_3SiCl	17
2	Me_2SiCl_2	35
3	$MeSiCl_3$	66
4	$PhSiCl_3$	61
5	$HSiCl_3$	65
6	$SiCl_4$	68

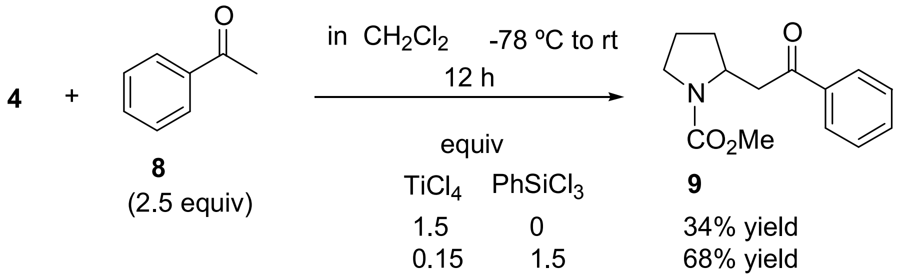
Next, we carried out some experiments to optimize amounts of $TiCl_4$ and $PhSiCl_3$ as a representative combination (Eq. 4), since the yields of **7** promoted by three trichlorosilanes and tetrachlorosilane were almost same (Table 1). The results are shown in Table 2. A combination of a catalytic (0.15 equiv) or an equimolar (1.5 equiv) amount of $TiCl_4$ and an equimolar amount of $PhSiCl_3$ could work well (entries 3 and 6).[8] On the other hand, a combination of an equimolar amount of $TiCl_4$ and a catalytic amount of $PhSiCl_3$ did not improve the yield (entry 5).

$$\mathbf{4} \quad + \quad \underset{(2.5\ \text{equiv})}{\mathbf{6}} \quad \xrightarrow[\text{in } CH_2Cl_2 \quad -78\ ^{\circ}C \text{ to rt} \quad 12\ \text{h}]{TiCl_4 + PhSiCl_3} \quad \mathbf{7} \qquad (4)$$

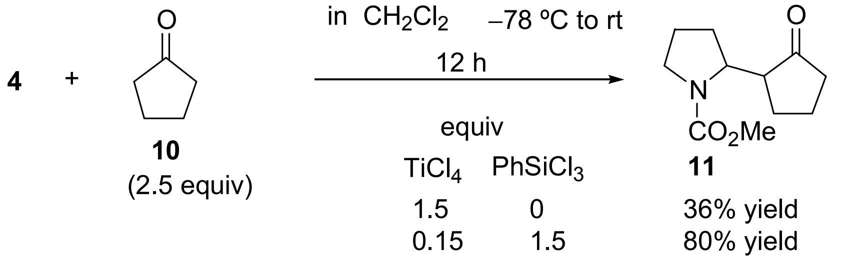
Similarly this combination of $TiCl_4$ (0.1 equiv) and $PhSiCl_3$ (1.5 equiv) could efficiently mediate the Mannich-type reaction of **4** with acetophenone **8** or cyclopentanone **10** to improve the corresponding products **9** and **11**[9] (Eqs. 5 and 6).

Table 2. Effect of amount of $TiCl_4$ and $PhSiCl_3$ on the reaction of **4** with **6**.

Entry	Equiv of $TiCl_4$	Equiv of $PhSiCl_3$	Yield (%) of **7**
1	0	1.5	3
2	0.15	0.15	2
3	0.15	1.5	61
4	1.5	0	23
5	1.5	0.15	34
6	1.5	1.5	61



(5)



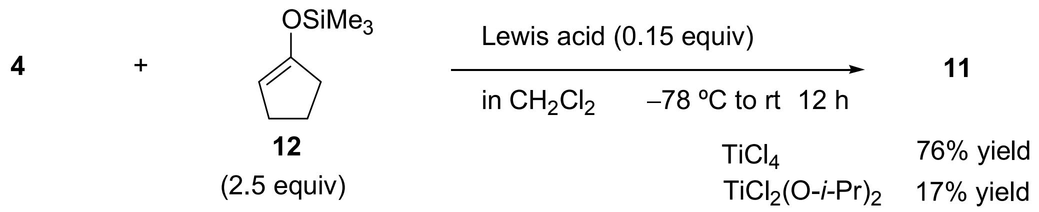
(6)

Similar improvement was accomplished in the case of using $TiCl_2(O\text{-}i\text{-}Pr)_2$ as a Lewis acid. Although using only $TiCl_2(O\text{-}i\text{-}Pr)_2$ did not proceed a reaction of **4** with **10**, a combination of $TiCl_2(O\text{-}i\text{-}Pr)_2$ and $PhSiCl_3$ could mediate the reaction of **4** with **10** to afford **11** in moderate yield (Eq. 7).

$$\mathbf{4} + \underset{(2.5\text{ equiv})}{\mathbf{10}} \xrightarrow[\text{equiv}]{\text{in } CH_2Cl_2 \quad -78\ ^{\circ}C \text{ to rt} \quad 12\text{ h}} \mathbf{11} \qquad (7)$$

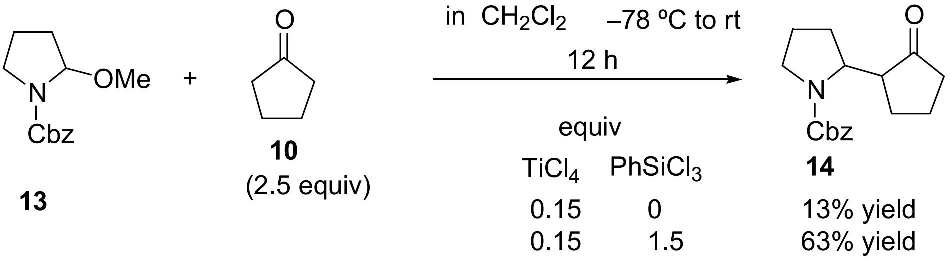
$TiCl_2(O\text{-}i\text{-}Pr)_2$	$PhSiCl_3$	
0.15	0	0% yield
0.15	1.5	65% yield

The yields of the reaction of **4** with **10** using a combination of Lewis acid and $PhSiCl_3$ shown in Eqs. 6 and 7 exceeded that of the reaction of **4** with trimethylsilyl enol ether **12** (Eq. 8).



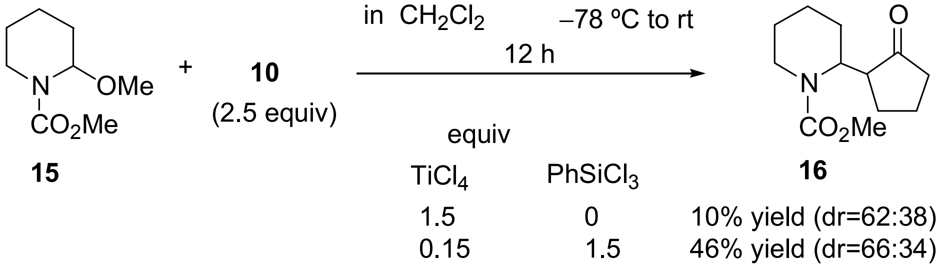
(8)

Also, the Mannich-type reaction of *N*-benzyloxycarbonylated pyrrolidines **13** with **10** was effectively mediated by a combination of $TiCl_4$ and $PhSiCl_3$ to afford the corresponding product **14**[8] (Eq. 9).

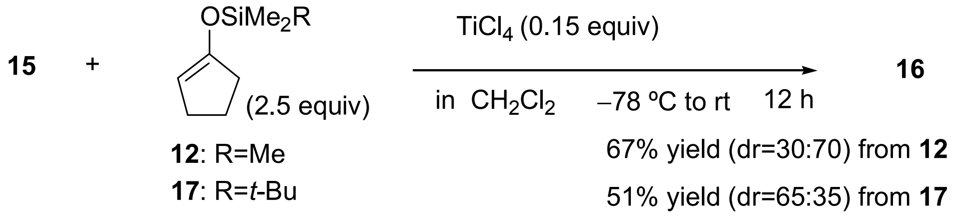


(9)

Piperidine derivative **15** reacted with **10** in the presence of $PhSiCl_3$ to give the corresponding coupling product **16** with moderate yield (Eq. 10). The diastereomer ratio 66:34 of **16** was almost same as that of **16** obtained from *t*-butyldimethylsilyl enol ether **17**, while that of **16** obtained from **12** was opposite (Eq. 11).[10]

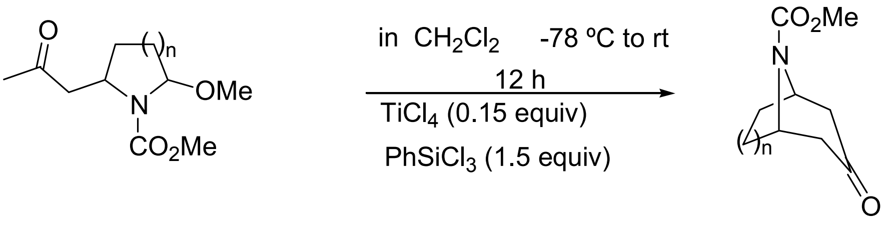


(10)



(11)

Furthermore, a combination of $TiCl_4$ and $PhSiCl_3$ effectively mediated the intramolecular Mannich-type reaction of *N*-methoxycarbonylated pyrrolidines **18a** (n=1) and its piperidine analogue **18b** (n=2) to form tropinone skeleton **19a** and its [3.3.1] analogue **19b** which is a precursor for alkaloid and redox-catalysts (Eq. 12).[11]



(12)

18a: n=1
18b: n=2

19a: n=1; 58% yield
19b: n=2; 40% yield

The role of the trichlorosilanes and tetrachlorosilane in the present system is not clarified at present. We presume that trichlorosilanes and tetrachlorosilane facilitates smooth enolate generation. Another possibility is that they may facilitate intermediary formations of enol silyl ethers.[5,6] However, this speculation could be ruled out, because these species can hardly be generated under the present acidic conditions.

CONCLUSION

In conclusion, a combination of $TiCl_4$ and $PhSiCl_3$ conducts the Mannich type reaction of *N*,*O*-acetals with ketones, wherein $PhSiCl_3$ acts as an efficient promoter. Although mechanistic details are still not clear, this reaction is a very promising method in organic synthesis.

EXPERIMENTAL

All commercial materials were used without further purification unless otherwise stated. Analytical thin layer chromatography was performed on Merck silica gel 60 F_{254} plates (0.25mm). Compounds were visualized by deeping in anisaldehyde followed by heating. Liquid chromatography was performed using indicated solvent on silica gel 60 (200-300 mesh). IR spectra were obtained on a Shimadzu FTIR-8100A. ^{1}H NMR spectra were obtained on Varian Gemini 300 and 400 MHz spectrometer and are reported in parts per million (δ) with tetramethylsilane (TMS) as the internal standard. The coupling constants are recorded in hertz.

A combination of TiC_4- and $PhSiCl_3$-mediated Mannich-type reaction: Typical procedure

Under a nitrogen atmosphere, $TiCl_4$ (12 μL, 0.15 mmol) and phenyltrichlorosilane (240 μL, 1.5 mmol) were added dropwise to the solution of **4** (159 mg, 1.0 mmol) and acetone (183 μL, 2.5 mmol) in CH_2Cl_2 (5 mL) at −78 °C. The resulting mixture was stirred for 12 h and allowed to stand until it warmed to room temperature. The solution was poured in ice water (10 mL) and extracted with $CHCl_3$ (10 mL x 3). The combined organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane : AcOEt = 10 : 1) to afford **7** as a colorless oil (112 mg, 61%). Compounds **7**,[4] **9**,[4] **19a**,[4] and **19b**[12] are known.

1-Methoxycarbonyl-2-(2-oxocyclopentyl)pyrrolidine (11)

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.40-2.50 (m, 10H), 2.70-3.05 (m, 1H), 3.25-3.50 (m, 2H), 3.65 and 3.68 (2s, 3H), 4.10-4.30 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 218.49 (1C), 155.11 (1C), 56.71, 56.94, 51.82, 51.48, 46.86, 46.54 , 38.42, 34.10, 32.34, 30.33, 27.51, 24.62, 20.25; IR (neat) 2974, 2880, 1747, 1713, 1464, 1396, 1207, 1124, 747 cm^{-1}. Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54, H, 8.11; N, 6.63. Found: C, 62.62, H, 8.11; N, 6.37.

1-Benzyloxycarbonyl-2-(2-oxocyclopentyl)pyrrolidine (14)

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.40-2.40 (m, 11H), 3.30-3.63 (m, 2H), 4.10-4.30 (m, 1H), 5.00-5.18 (m, 2H), 7.20-7.42 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 218.88, 218.75, 154.82, 154.59, 136.51, 128.23, 66.38, 56.93, 56.12, 51.98, 51.59, 46.79, 46.70, 38.60, 38.26, 30.50, 28.43, 27.69, 25.48, 24.81, 20.36, 20.15; IR (neat) 3374, 3090, 2963, 2880, 1736, 1705, 1597, 1498, 1454, 1419, 1288, 1134 cm^{-1}. HRMS. Calcd for $C_{17}H_{21}NO_3$: 287.1522. Found: 287.1525.

1-Methoxycarbonyl-2-(2-oxocyclopentyl)piperidine (16)

More polar diastereomer (minor isomer in Eq. 10): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.30-2.60 (m, 13H), 2.99 (t, *J*=9.9Hz, 1H), 3.65 and 3.68 (2s, 3H), 3.95-4.30 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 218.56, 156.93, 52.10, 51.62, 45.19, 39.85, 38.48, 28.16, 26.81, 24.74, 20.39, 18.54; IR (neat) 2947, 2864, 1732, 1693, 1446, 1263, 1180, 767 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98, H, 8.50; N, 6.22. Found: C, 64.00, H, 8.46; N, 6.19.

Less polar diastereomer (major isomer in Eq. 10): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.30-2.40 (m, 12H), 2.53-2.80 (m, 2H), 3.68 (s, 3H), 3.93-4.40 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 219.03, 155.76, 52.18, 50.30, 46.81, 39.57, 38.51, 26.61, 26.08, 24.85, 19.78, 18.47; IR (neat) 2939, 2864, 1732, 1693, 1446, 1410, 1263, 1186, 1153, 767 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98, H, 8.50; N, 6.22. Found: C, 64.19, H, 8.42; N, 6.33.

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8. Although big activation of acetone with a combination of $TiCl_4$ (1.0 equiv) and $PhSiCl_3$ (1.0 equiv)

was observed by ^{1}H-NMR analyses shown below, enolization of acetone could not be proved. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.18 for acetone; 2.24 for acetone with $TiCl_4$ (1.0 equiv); 2.17 for acetone with $PhSiCl_3$ (1.0 equiv); 2.66 for acetone with a combination of $TiCl_4$ (1.0 equiv) and $PhSiCl_3$ (1.0 equiv).

9. Two diastereomers of **11** were not separable by SiO_2 column chromatography. Also, the diastereomer ratio of **11** could not be determined by NMR, HPLC or GC. Similarly, the diastereomer ratio of **14** could not be determined.
10. The diastereomer ratios of **16** shown in Eqs. 10 and 11 might suggest the formation of sterically hindered silyl enol ether from **10** and $PhSiCl_3$.
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