Acylation of 1-[2-(2-Methoxyethoxy)ethyl]pinacolone: Preparation of 4-[2-(2-Methoxyethoxy)ethyl]-2,2,6,6-tetramethylheptane-3,5-dione

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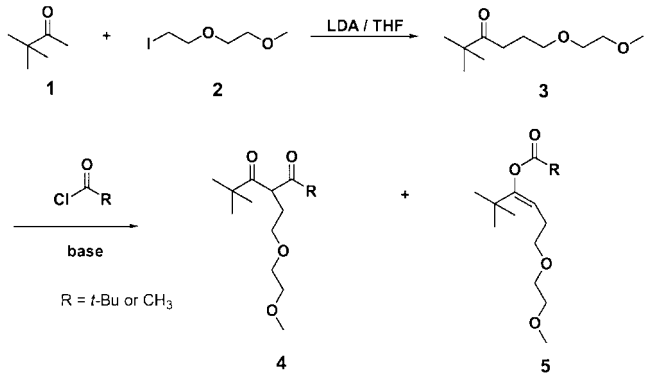
Substituted or non-substituted 2,2,6,6-tetramethylheptane-3,5-dione (TMHD) has been used as a ligand of a precursor to the chemical vaporization of deposition (CVD).[1,2] α-Alkyation of β-diketones is generally a very slow reaction, affording low yields due to serious competition from *O*-alkylation.[3,5] When activated electrophiles, such as allyl bromide, propargyl bromide, or benzyl bromide,[4,5] react with acetylacetone, the yield of *C*-alkylation is exceptionally good; however, reactions of highly substituted β-diketone with long chained electrophiles show very low yields of *C*-alkylated products.[6] Moreover, alkylation of TMHD itself has no examples. We examined the direct alkylation of TMHD with 2-(2-methoxyethoxy)ethyl iodide under various conditions, and we found no reaction occurred at all even after 3 days heating in THF or DMF with bases such as sodium hydride, sodium carbonate, potassium carbonate, or cesium carbonate.[7] To synthesize 4-[2-(2-methoxyethoxy)-ethyl]-2,2,6,6-tetramethylheptane-3,5-dione (**4**) we should detour[8,9] as shown in Scheme 1. Pinacolone (**1**) was mono-alkylated by 2-(2-methoxyethoxy)ethyl iodide (**2**) with lithium diisopropylamide (LDA) as a base to form [2-(2-methoxyethoxy)ethyl]-2,2-dimethylbutan-3-one (**3**) in good yield. To acylate **3**[10] by trimethylacetyl chloride, we first used LDA as a base at -78 °C in THF. After the reaction mixture was stirred at -78 °C for 2 h, we isolated twice the amount of *O*-acylated product **5**[11] compared with *C*-acylated product **4**[12] in a total yield 69% (Entry 1 in Table 1). We examined lithium bis(trimethylsilyl)amide (lithium HMDS), sodium bis(trimethylsilyl)amide (sodium HMDS), potassium bis(trimethylsilyl)amide (potassium HMDS), and sodium hydride as bases under the same reaction conditions (Table 1). *O*-Acylations of **3** were favored slightly in this acylation, but when potassium HMDS was used as a base, *C*-acylation was favored to a small extent (Entry 4 and 8 in Table 1). In the case of sodium hydride, almost no reaction occurred even at rt (Entry 5 in Table 1). The addition of cesium carbonate or substitution of solvent to toluene showed no significant effects in the percentage of *O*-acylation and *C*-acylation. We examined the acylation of **3** with acetyl chloride instead of trimethylacetyl chloride to investigate the effect of the bulkiness of electrophiles, and we found *C*-alkylation was more favored as expected (Entry 10, 11, and 12 in Table 1). When potassium HMDS was used as a base in toluene, the best result was obtained in acetylation and also good result in trimethylacetylation. But, we prefer THF due to the easy removal of solvent in the purification process. Next, we changed the electrophile from trimethylacetyl chloride to the corresponding cyanide,[13,14] anhydride, or ester to change the softness of the electrophiles. Under the same reaction conditions, we applied a different set of electrophiles in THF, and the results are summarized in Scheme 2 and Table 2. When trimethylacetyl cyanide was used as an electrophile, significantly improved results were obtained (Entry 1 and 2 in Table 2).[15] When potassium

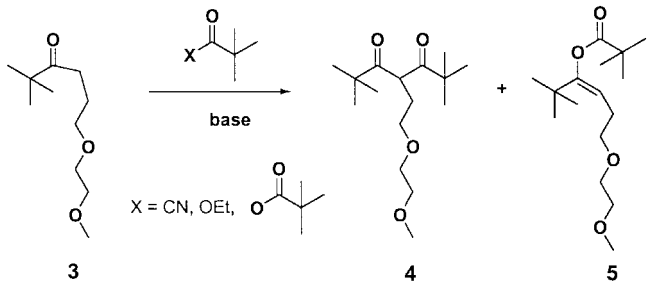


Scheme 1

Table 1. Acylation of 4-[2-(2-Methoxyethoxy)ethyl]-2,2-dimethyl-butan-3-one (**3**) by Trimethylacetyl Chloride or Acetyl Chloride with Various Bases

Entry	R	Base	Reaction temperature/Solvent	**4** (%)[a]	**5** (%)[a]
1	*t*-Bu	LDA	-78 °C/THF	24	45
2	*t*-Bu	Lithium HMDS	-78 °C/THF	30	39
3	*t*-Bu	Sodium HMDS	-78 °C/THF	<10	<10
4	*t*-Bu	Potassium HMDS	-78 °C/THF	42	36
5	*t*-Bu	Sodium hydride	24 °C/THF	trace	trace
7	*t*-Bu	Lithium HMDS	-78 °C/Tolune	26	67
8	*t*-Bu	Potassium HMDS	-78 °C/Toluene	35	27
9	*t*-Bu	Lithium HMDS/ cesium carbonate	-78 °C/Toluene	26	20
10	CH_3	Lithium HMDS	-78 °C/THF	32	31
11	CH_3	Potassium HMDS	-78 °C/THF	51	30
12	CH_3	Potassium HMDS	-78 °C/Toluene	53	14

[a]Isolated yields



Scheme 2

Table 2. Acylation of 4-[2-(2-Methoxyethoxy)ethyl]-2,2-dimethylbutan-3-one (**3**) by Various Electrophiles

Entry	X	Base	Reaction Temperature/Solvent	**4** (%)[a]	**5** (%)[a]
1	CN	Lithium HMDS	-78 °C/THF	74	17
2	CN	Potassium HMDS	-78 °C/THF	80	9
3	OCOBu-*t*	Lithium HMDS	-78 °C/THF	54	6
4	OCH_2CH_3	Lithium HMDS	-78 °C/THF	trace	trace

[a]Isolated yields

HMDS was used as a base, the yield of *C*-acylation increased to 80% and the ratio of *C*-acylation to **3** was much improved to 9 : 1 in total 89% isolated yield (Entry 2 in Table 2). Even when lithium HMDS was used as a base, *C*-alkylation was much more favored (Entry 1 in Table 2) than with trimethylacetyl chloride (Entry 2 in Table 1). Reaction with anhydride also showed improved results compared with acid chloride (Entry 3 Table 2), whereas ester did not react at all (Entry 4 in Table 2).

4-[2-(2-Methoxyethoxy)ethyl]-2,2,6,6-tetramethylheptane-3,5-dione (**4**), which is expected to be useful as a ligand of a precursor in CVD was synthesized from 4-[2-(2-methoxyethoxy)ethyl]-2,2-dimethylbutan-3-one (3) and trimethylacetyl cyanide with potassium HMDS as a base in good yield. We will synthesize other derivatives by this procedure and test the resulting compounds as ligands of precursors.

References

1. Kirsty, A. F.; O'Brien, P.; Otway, D. J.; White, A. J. P.; Williams, D. J.; Jones, A. C. *Inorg. Chem.* **1999**, *38*, 1432.
2. Beachley, O. T., Jr.; James, R. G.; Churchill, M. R. *Organometallics* **2000**, *19*, 4544.
3. Kurts, A. L.; Genkina, N. K.; Maclas, A.; Beletskaya, I. P.; Reutov, O. A. *Tetrahedron* **1971**, *27*, 4777.
4. Lloris, M. E.; Galvez, N.; Marquet, J.; Moreno-Manas, M. *Tetrahedron* **1991**, *47*, 8031.
5. Ranu, B. C.; Bhar, S. *J. Chem. Soc. Perkin Trans. I* **1992**, *3*, 365.
6. Zanina, A. S.; Shergina, S. I.; Sokolov, I. E.; Shvartsberg, M. S. *Izv. Akad. Nauk., Ser. Khim.* **1996**, *10*, 2518.
7. Shrout, D. P.; Lightner, D. A. *Synth. Commun.* **1990**, *20*, 2075.
8. Tirpak, R. E.; Rathke, M. W. *J. Org. Chem.* **1982**, *47*, 5099.
9. (**3**): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.03-1.07 (m, 9H), 1.75-1.81 (m, 2H), 2.21-2.60 (m, 2H), 3.31 (s, 3H), 3.36-3.48 (m, 6H); IR (cm^{-1}) 1107, 1479, 1705, 2873, 2966.
10. (**5**, **R** = *t*-butyl): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.05-1.32 (m, 18H), 2.08 (q, *J* = 14.04 Hz, 2H), 3.38-3.57 (m, 9H), 5.12 (s, 1H); ^{13}C NMR δ 26.35, 27.32, 27.92, 26.18, 39.15, 59.00, 69.83, 70.19, 71.85, 109.13, 155.78, 175.59; IR (cm^{-1}) 1122, 1747, 2873, 2972; HRMS calcd for $C_{16}H_{31}O_4$ (MH^+) 287.2218, found 287.2222. (**5**, **R** = methyl): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.03-1.13 (m, 9H), 2.07-2.16 (m, 5H), 3.33-3.57 (m, 9H), 5.12 (t, *J* = 14.04 Hz, 1H); ^{13}C NMR δ 20.61, 26.39, 26.71, 27.93, 30.91, 36.02, 59.05, 69.92, 70.16, 71.87, 109.36, 156.03, 168.43; IR (cm^{-1}) 1207, 1758, 2872, 2969; HRMS calcd for $C_{13}H_{25}O_4$ (MH^+) 245.1757, found 245.1753.
11. (**4**, **R** = *t*-butyl): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.11-1.29 (m, 18H), 2.07 (q, *J* = 6.51 Hz, 2H), 3.28-3.35 (m, 5H), 3.48 (t, *J* = 7.52 Hz, 4H), 4.71 (t, *J* = 13.02 Hz, 1H); ^{13}C NMR 27.26, 29.41, 30.91, 44.57, 51.76, 58.99, 68.94, 70.09, 71.84, 210.93; IR (cm^{-1}) 1105, 1691, 1719, 2874, 2966; HRMS calcd for $C_{16}H_{31}O_4$ (MH^+) 287.2223, found 287.2222. (**4**, **R** = methyl) ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.14 (s, 9H), 2.17 (s, 3H), 3.36 (s, 3H), 3.42-3.62 (m, 8H), 4.38 (t, *J* = 8.90 Hz, 1H); ^{13}C NMR δ 26.40, 27.27, 29.42, 44.59, 51.78, 59.01, 68.96, 69.87, 70.10, 71.82, 210.93; IR (cm^{-1}) 1105, 1479, 1720, 2873, 2964.
12. Tang, Q.; Sen, S. E. *Tetrahedron Lett.* **1998**, *39*, 2249.
13. Sperber, N.; Fricano, R. *J. Am. Chem. Soc*. **1950**, *72*, 2792.
14. Kraus, G. A.; Dneprovskaia, E. *Tetrahedron Lett.* **2000**, *41*, 21.
15. Reaction of [2-(2-methoxyethoxy)ethyl]-2,2-dimethylbutan-3-one (**3**) with trimethylacetyl cyanide. To a solution of [2-(2-methoxyethoxy)ethyl]-2,2-dimethylbutan-3-one (3) (0.50 g, 2.47 mmol) in anhydrous THF (25 mL) at -78 °C was added potassium bis(trimethylsilyl)amide (0.5 M solution in toluene, Aldrich, 7.41 mL) and the reaction mixture was stirred for 2 h. And then, trimethylacetyl cyanide (0.41 g, 3.71 mmol) was dropwisely added by a syringe. After being stirred for 2 h, the reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, concentrated under reduced pressure, and the residue was purified by chromatography on silica gel (EtOAc/Hexane, 4/1) to give (**4**) (0.57 g, 80%) and (**5**) (0.06 g, 9%) as a pale yellow oil.