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PREPARATION OF FUNCTIONALIZED α **-CHLOROMETHYL**

KETONES USING RIEKE ZINC

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Abstract: The cross-coupling reaction of highly functionalized organozinc reagents with chloroacetyl chloride mediated by copper allows for the easy preparation of functonalized α -chloromethyl ketones in excellent yields.

When we first reported our method of zinc activation in 1973, we demonstrated for the first time the ability of Rieke zinc to undergo oxidative addition to alkyl and aryl bromides.¹ Recently, we reported an improved method for the preparation of Rieke zinc, which was not only easier and safer but also yielded a more reactive zinc.² This Rieke zinc allowed direct oxidative addition to highly functionalized alkyl, aryl, and vinyl bromides, as well as the corresponding iodides. The utility of these organozinc reagents were further demonstrated by

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using a soluble copper cyanide/lithium bromide complex³ to mediate the crosscoupling with acid chlorides in high yields.

 α -Chloromethyl ketones are useful synthetic reagents in organic synthesis. However, it is difficult to prepare α -chloromethyl ketones via direct chlorination of methyl ketones. Thus, much work has been done to develope alternate methods of synthesis. However, many of these procedures require the use of organometallic reagents that preclude the presence of secondary functional groups.⁴ Other methods require oxidizing agents⁵ or conditions which can promote rearrangements.⁶ Therefore, we would like to report a simple straightforward method for the preparation of α -chloromethyl ketones under extremely mild conditions. Using Rieke zinc prepared by the reduction of ZnCl₂ in THF with lithium naphthalenide, we have found that alkyl and aryl bromides readily undergo oxidative addition yielding the corresponding organozinc bromides. These organozinc reagents smoothly cross-couple with chloroacetyl chloride mediated by the soluble copper cyanide/lithium bromide complex as shown in Table 1.

Scheme

1

$$CH_{3}(CH)_{5}Br + Zn^{*} \rightarrow CH_{3}(CH)_{5}ZnBr \xrightarrow{CuCN-LiBr}_{-35^{\circ}C} CH_{3}(CH)_{5}$$

As shown in Scheme 1, 1-bromohexane reacts cleanly with Rieke zinc to give the organozinc, which when catalyzed by copper cross-couples with chloroacetyl chloride in 75 % isolated yield. Signigicantly, a number of functional groups will tolerate these reaction conditions. Respectable yields were obtained with alkyl as well as aryl nitriles and esters. Additional studies are underway to more fully explore the full synthetic utility of the reaction.

Experimental: Infrared spectra were taken on a Analect RFX-65 FTIR spectrophotometer, neat on NaCl plates. ¹H NMR were obtained on a General Electric Ω -300 spectometer. All shifts are reported in parts per million downfield from an internal tetramethlysilane standard. Fully decoupled ¹³C NMR spectra were also obtained on a General Electric Ω -300 spectometer. The center peak of CDCl₃, 77.0 ppm, was used as an internal reference. Elemental analysis were preformed by Desert Analytics (Tucson, AZ). All inert atmosphere manipulations were carried out on a dual manifold vacuum/argon system. Linde prepurified grade argon was further purified by passing it through several columns containing a 150 °C BASF R3-11 catalyst, phosphorus pentoxide, and granular potassium hydroxide. Tetrahydrofuran was distilled prior to use from sodium/potassium alloy under an argon atmosphere. All other reagents were used as received from the manufacturer. All organozinc reagents, including the arylzinc, were formed at room temperature. Reaction times varied from 20 min for alkyl bromides to 1 h.

Entry.	RX	Products ^a	Yield % ^b
1	CH ₃ (CH ₂) ₅ Br	CH3(CH)5 CI	75
2	CH ₃ (CH ₂) ₇ Br	CH ₃ (CH) ₇ CI	74
3	CH ₃ (CH ₂) ₉ Br	CH3(CH)3 CI	72
4	NC	NC	52
5	NC Br	NC	86
6	NC Br	NC	81
7	Et ^O Br		87
8	Jowen Br	Jord CI	60
9	Br	CI CN	85

Table 1. Reaction of Organozinc Reagent Mediated by Copper with

Chloroacetyl Chloride.



a) All products are characterized by ¹H NMR, ¹³C NMR, IR, and HRMS. b) Isolated yield.

30 min for the aryl bromides. A typical procedure for products reported here is as follows.

1-Chloro-6-cyano-2-hexanone: (Table 1, entry 5). Lithium (29.12 mmol) and naphthalene (2.92 mmol) in freshly distilled THF (13 mL) were stirred under argon until the green color indicating the formation of lithium naphthalenide appeared (ca. 30 sec.). ZnCl₂ (14.11 mmol) in 15 mL THF was cannulated dropwise into the lithium naphthalenide taking care to maintain the green color. After the transfer was complete the Rieke zinc was stirred for 30 min and allowed to settle (ca. 2 hr). The supernatant was cannulated off and replaced with fresh THF. In some reactions the active zinc was purchased form Rieke Metals Inc. and had been stored in bottles for 6 months. 4-Bromobenzonitrile (10.91 mmol) was added neat via syringe and stirred for 30 min before the excess zinc was allowed to settle. A solution of CuCN (2.83 mmol) and LiBr (3.82 mmol) was dissolved in 10 mL of THF and cooled to -40 °C. The RZnBr was cannulated into the CuCN solution, taking care not to transfere any active zinc, and the chloroacetyl chloride (9.40 mmols) was added neat via syringe. The reaction was warmed to room temperature with stirring and quenched with NH₄Cl. The aqueous layer was extracted with diethyl ether (3 x 30mL) and the combined organic layers dried over MgSO₄. Removial of solvent and flash chromatography on silica gel afforded 1-chloro-6-cyano-2-hexane (1.179g, 86% yield): ¹H NMR δ 4.13 (s 2H), 2.82-2.78 (t 2H), 2.48-2.43 (t 2H), 2.02-1.93 (m 2H); ¹³C NMR δ 200.9, 118.8, 47.8, 37.3, 19.0, 16.1; IR 2942, 2246, 1735 cm⁻¹; HRMS calcd for C₆H₈ONCl 145.0294, found 145.0293. Anal. Calcd. for C: 49.50, H: 5.54, N: 9.62, found C: 49.10, H: 5.66, N: 9.30.

1-chloro-2-octanone: (Table 1, entry 1) ¹H NMR δ 4.05 (s 2H), 2.58-2.53 (t 2H), 1.60-1.56 (t 2H), 1.28 (br s 6H), 0.87-0.83 (t 3H); ¹³C NMR δ 202.7, 48.1, 39.6, 31.4, 28.6, 23.5, 22.3, 13.9; IR 2954, 2927, 2854, 1735, 1722 cm⁻¹.

1-chloro-2-decanone: (Table 1, entry 2) ¹H NMR δ 4.06 (s 2H), 2.60-2.54 (t 2H), 1.62-1.57 (t 2H), 1.25 (br s 10H), 0.88-0.84 (t 3H); ¹³C NMR δ 202.7, 48.1, 39.7, 31.7, 29.2, 29.0, 28.9, 23.6, 22.6, 13.9.

1-chloro-2-dodecanone: (Table 1, entry 3) ¹H NMR δ 4.04 (s 2H), 2.55-2.50 (t 2H), 1.58-1.53 (t 2H), 1.21 (br s 14H), 0.84-0.79 (t 3H); ¹³C NMR δ 202.7, 48.0, 39.5, 31.7, 29.4, 29.3, 29.2, 19.1, 28.9, 23.5, 22.5, 13.9; IR 2952, 2925, 2854, 1722, 1465, 1405 cm⁻¹. **1-Chloro-5-cyano-2-pentane:** (Table 1, entry 4) ¹H NMR δ 4.11 (s 2H), 3.00-2.96 (t 2H), 2.61-2.56 (t 2H); ¹³C NMR δ 199.1, 118.5, 47.4, 35.0, 11.3; IR 2979, 2940, 2250, 1739 cm⁻¹; HRMS calcd for C₃H₆ONCl 131.0138, found 131.0138.

1-Chloro-7-cyano-2-heptanone: (Table 1, entry 6) ¹H NMR δ 4.04 (s 2H), 2.63-2.59 (t 2H), 2.35-2.30 (t 2H), 1.77-1.59 (m 4H); ¹³C NMR δ 201.5, 119.2, 47.9, 38.3, 24.5, 22.2, 16.8; IR 2940, 2875, 2246, 1733 cm⁻¹; HRMS calcd for C₇H₁₀ONCl 159.0451, found 159.0451 Anal. Calcd. for C: 5282, H: 6.34, N: 8.80, found C: 52.61, H: 6.44, N: 8.50.

Ethyl-6-chloro-5-oxo-hexanoate: (Table 1, entry 7) ¹H NMR δ 4.18-4.07 (m 4H), 2.73-2.66 (t 2H), 2.36-2.32 (t 2H), 1.97-1.89 (m 4H), 1.29-1.22 (t 3H); ¹³C NMR δ 201.5, 172.6, 60.1, 47.9, 38.2, 32.7, 18.4, 13.9; IR 2983, 2984, 2908, 1727; HRMS calcd for C₈H₁₃O₃Cl 192.0553, found 192.0553.

6-Chloro-5-oxo-hexyl acetate: (Table 1, entry 8) ¹H NMR δ 4.05-4.00 (m 4H), 2.63-2.58 (t 2H), 2.00 (s 3H), 1.69-1.61 (m 4H); ¹³C NMR δ 202.1, 170.9, 63.8, 48.0, 38.8, 27.6, 20.8, 19.7; IR 2954, 2898, 2875, 1735 cm⁻¹; HRMS calcd for C₈H₁₃O₃Cl 192.0553, found 192.0553.

o-cyano-alpha-chloroacetophenone: (Table 1, entry 9) ¹H NMR δ 7.97-7.74 (m 4H), 4.73 (s 2H); ¹³C NMR δ 190.2, 136.8, 135.4, 133.2, 132.7, 129.9, 117.4, 111.5, 46.1; IR 2958, 2927, 2229, 1733 cm⁻¹; HRMS calcd for C₈H₆ONCl 167.0138, found 179.0138. *p*-cyano-alpha-chloroacetophenone: (Table 1, entry 10) ¹H NMR δ 8.06-8.03 (d 2H), 7.81-7.78 (d 2H), 4.71 (s 2H); ¹³C NMR δ 205.1, 134.0, 133.5, 133.4, 118.7, 111.9, 45.0; IR 3066, 2958, 2927, 2229, 1733 cm⁻¹; HRMS calcd for C_oH₆ONC1 179.0138, found 167.0138.

p-carbethoxy-alpha-chloroacetophenone: (Table 1, entry 11) ¹H NMR δ 8.17-8.13 (d 2H), 8.03-7.99 (d 2H), 4.75 (s 2H), 4.46-4.36 (m 2H), 1.45-1.38 (t 3H); ¹³C NMR δ 190.7, 165.3, 137.2, 134.9, 129.8, 128.8, 128.3, 61.5, 45.9, 14.2; IR 2958, 2927, 1712, 1278 cm⁻¹; HRMS calcd for C₁₁H₁₁O₃Cl 226.0397, found 226, 0397.

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References

- Rieke, R. D.; Hudnell, P. M.; Uhm, S. J. Chem. Soc., Chem. Comm. 1973, 269.
- 2. Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. J. Org. Chem. 1991, 56,1445.
- Knochel, P.; Yeh, M. L. P.; Berk, S. C.; Talbert, J. J. Org. Chem. 1988, 53, 2390.
- a) Mahatsekake, C.; Catel, J. M.; Andrieu, C. G.; Ebel, M.; Mollier, Y.; Tourillon, G. Phosphorus, Sulfur, Silicon Relat. Elem. 1990, 47, 35. b) Tarhouni, R.; Kirschleger, B.; Rambaud, M.; Villieras, J. Tetrahedron Lett. 1984, 25, 835. c)Reutrakul, V.; Kanghae, W. Tetrahedron Lett. 1977, 14, 1225.
- 5. Lee, J. G.; Ha, D. S. Tetrahedron Lett. 1989, 30, 193.
- 6. Kimpe, N. D.; Cock, W. D.; Schamp, N. Synthesis, 1987, 188.

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