An Improved Method for the Addition Reactions of 1,3-Dichloroacetone with Combined Organolithium-Cerium Trichloride Reagents

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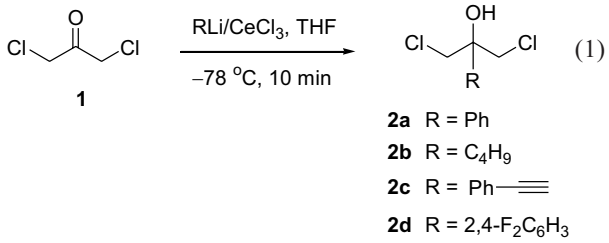
Alkyl-, phenyl- and alkynyllithium reagents in combination with anhydrous cerium(III) chloride underwent addition reactions with 1,3-dichloroacetone in a very efficient manner. The addition products are versatile precursors for 2-substituted epichlorohydrins and glycidols. Fluconazole, a potent antifungal agent, was thus synthesized in 67% yield by addition of 1,3-dichloroacetone to 2,4-difluorophenyllithium in the presence of cerium(III) chloride, followed by substitution of the chlorine atoms with 1,2,4-triazole.

Keywords: 1,3-Dichloroacetone; Organolithium reagents; Cerium(III) chloride; Fluconazole; Epichlorohydrins; Glycidols.

INTRODUCTION

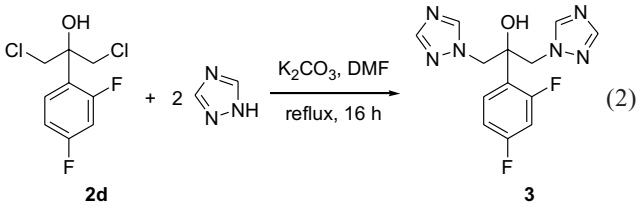
As 1,3-dichloroacetone (**1**) is a highly enolizable ketone, its addition reactions with basic organolithium and organomagnesium reagents may be complicated by side reactions such as deprotonation and reductive dechlorination reaction.[1] On the other hand, organolanthanoid reagents are known to be more oxophilic and less basic than organolithium and organomagnesium reagents.[2] The successful application of organolanthanoides, particularly organocerium reagents, to carbonyl addition reactions has been extensively investigated.[2] Along this line, we wish to report an improved procedure by using organolithium reagents together with cerium(III) chloride to achieve the addition reactions with 1,3-dichloroacetone.[1a,3] This method thus provided an expedient route to tertiary alcohols **2a-d** (equation 1).[4]



(1)

RESULTS AND DISCUSSION

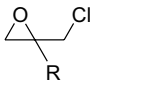
The required anhydrous $CeCl_3$ was prepared by heating the commercially available $CeCl_3$ heptahydrate at 140 °C *in vacuo* for at least 3 h. The organolithium reagent was premixed with $CeCl_3$ in THF under an atmosphere of argon, and 1,3-dichloroacetone was then added at -78 °C. The addition reaction was completed in 10 min to give high yields (84-96%) of the desired addition products **2a-d**. The yields decreased by adding organolithium reagents to the mixture of 1,3-dichloroacetone and $CeCl_3$. If the organolithium reagent (e.g. PhLi) was replaced by Grignard reagent (e.g. PhMgCl), the yield of addition product also decreased significantly (e.g. dropping from 96% to 62% in the case of **2a**). In the absence of $CeCl_3$, the addition reactions using either organolithium or Grignard reagents gave inferior yields as shown in the previous reports.[3] For example, our study showed a 96% yield of **2d** from the addition reaction of 1,3-dichloroacetone with the combined reagents of 2,4-difluorophenyllithium and $CeCl_3$. However, the yield of **2d** dropped to 64% when $CeCl_3$ was absent in the reaction.[3c]



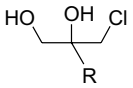
(2)

Fluconazole (**3**), 2-(2,4-difluorophenyl)-l,3-bis(1,2,4-triazol-l-yl)-2-propanol, is useful in treatment of topical infections in man caused by fungi such as the species of *Candida, Trichophyton, Microsporum, Epidermophyton, Cryptococcus, Aspergillus, Coccidiodes, Paracoccidiodes, Histoplasma,* and *Blastomyces*.[4] The antifungal activity is evaluated both *in vitro* and *in vivo*. For human use, fluconazole can be administered either orally or by injection. Fluconazole was introduced under the brand name of Diflucan®

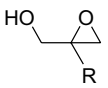
by the Pfizer Pharmaceutical Company in 1994. The previous syntheses of fluconazole had the drawback of low overall yields (< 35%).[4,5] As we had an easy access to the tertiary alcohol **2d** with 1,3-dichloro substituents, we investigated further the substitution reaction with 1,2,4-triazole (equation 2). After several modifications, we were able to obtain fluconazole in 70% yield by heating a mixture of **2d**, 1,2,4-triazole (2.2 equiv) and K_2CO_3 (2.2 equiv) in DMF solution. This sample of fluconazole, mp 138.5-140 °C (recrystallization from EtOAc/hexane) was pure and fully characterized. No contamination of the isomers derived by substitutions at the *N*-4 atoms of 1,2,4-triazoles was found as evidenced by the NMR analyses.[5c]



4a R = Ph
4c R = Ph—≡



5a R = Ph
5c R = Ph—≡



6a R = Ph

Epichlorohydrin is often utilized as a cross-linking agent for polymers. Treatments of the addition products **2a** and **2c** with *t*-BuOK at room temperature in *t*-BuOH solution gave 2-substituted epichlorohydrins **4a** and **4c** in 92% and 90% yields, respectively. The acid-catalyzed hydrolyses of **4a** and **4c** gave diols **5a** and **5c**. Compound **5a** was in turn treated with K_2CO_3 in MeOH to afford glycidol **6a**. The functional transformations and applications of 2-substituted epichlorohydrins and glycidols in organic synthesis have been explored.[3b,6]

In summary, we have found an efficient method to carry out the addition reactions of 1,3-dichloroacetone with alkyl-, phenyl- and alkynyllithium reagents by the mediation of an appropriate lanthanoid Lewis acid $CeCl_3$. The versatile uses of these addition products have been demonstrated by the synthesis of fluconazole and transformations to epichlorohydrins and glycidols.

EXPERIMENTAL

Melting points are uncorrected. Tetramethylsilane (δ_H = 0 ppm) and $CDCl_3$ (δ_C = 77.0 ppm for the central line of triplet) were used as internal standards in ^1H and ^{13}C NMR spectra, respectively. Mass spectra were recorded at an ionizing voltage of 70 or 20 eV. Silica gel 60F sheets were used for analytical thin-layer chromatography. Column chromatography was performed on SiO_2 (70-230 mesh); gradients of EtOAc and hexane were used as eluents. The reagents and solvents were dried according to standard procedure.

1,3-Dichloro-2-phenyl-2-propanol (2a)[1a,3b]

A sample of $CeCl_3 \cdot 7\ H_2O$ (5.58 g, 15 mmol) was dried at 140 °C *in vacuo* for at least 3 h, cooled under an argon atmosphere, and anhydrous tetrahydrofuran (THF, 75 mL) was added. The suspension was stirred at room temperature for 4 h, cooled to -78 °C in a dry ice-acetone bath, and a solution of phenyllithium (10.1 mmol, 5.50 mL of 2 M cyclohexane-ether solution) was added dropwise over a period of 5 min. The mixture was stirred at -78 °C for 40 min; a solution of 1,3-dichloroacetone (1.27 g, 10 mmol) in THF (5 mL) was added rapidly. After which, the mixture was stirred for 10 min at -78 °C, and quenched by addition of aqueous acetic acid solution (10%, 1 mL). The mixture was diluted with brine (15 mL), and extracted with ethyl acetate (EtOAc, 3 × 20 mL). The combined extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated by rotary evaporation, and the residue was purified on a silica gel column by elution with EtOAc/hexane (2:98) to give the title compound (1.96 g, 96% yield based on 1,3-dichloroacetone). Oil; TLC (EtOAc/hexane (2:98)) R_f = 0.12; IR (neat) 3552, 3034, 2967, 1176, 1071 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.91 (1H, s), 3.89 (2H, d, *J* = 11.5 Hz), 3.96 (2H, d, *J* = 11.5 Hz), 7.35-7.51 (5H, m); MS *m/z* (rel intensity) 204 (1, M^+), 155 (100); HRMS calcd for $C_8H_8{}^{35}ClO$ (M^+ - CH_2C1) 155.0263, found *m/z* 155.0236.

1-Chloro-2-(chloromethyl)-2-hexanol (2b)[3b]

A suspension of anhydrous $CeCl_3$ (2.47 g, 10 mmol) in THF (50 mL) was placed in a round-bottomed flask (100 mL) and stirred at room temperature for 4 h. The suspension was cooled to -78 °C in a dry ice-acetone bath; a solution of butyllithium (10 mmol, 6.25 mL of 1.6 M hexane solution) was added dropwise over a period of 5 min. The mixture was stirred at -78 °C for 40 min; a solution of 1,3-dichloroacetone (1.27 g, 10 mmol) in THF (5 mL) was added rapidly. After which, the mixture was stirred for 10 min at -78 °C, and quenched by addition of aqueous acetic acid solution (10%, 1 mL). The mixture was worked up as usual to give the title compound (1.56 g, 84% yield). Oil; TLC (EtOAc/hexane (1:9)) R_f = 0.25; IR (neat) 3446, 2956, 1028 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.2 Hz), 1.38-1.29 (4H, m), 1.66-1.57 (2H, m), 2.36 (1H, br s, OH), 3.53 (2H, d, *J* = 11.2 Hz), 3.62 (2H, d, *J* = 11.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 22.9, 24.7, 34.6, 48.3 (2 ×), 73.7; MS *m/z* (rel intensity) 167 (1), 135 (100); HRMS calcd for $C_6H_{12}{}^{35}ClO$ (M^+ - CH_2C1) 135.0576; found *m/z* 135.0582.

1-Chloro-2-(chloromethyl)-4-phenyl-3-butyn-2-ol (2c)

A solution of phenylacetylene (1.07 g, 10.5 mmol) in THF (10 mL) was treated with butyllithium (10.8 mmol, 6.75

mL of 1.6 M hexane solution) at 0 °C for 30 min. The prepared (phenylethynyl)lithium solution was added dropwise to a suspension of anhydrous $CeCl_3$ (3.70 g, 15 mmol) in THF (60 mL) at -78 °C. The mixture was stirred at -78 °C for 40 min; a solution of 1,3-dichloroacetone (1.27 g, 10 mmol) in THF (5 mL) was added rapidly. After which, the mixture was stirred for 10 min at -78 °C, and quenched by addition of aqueous acetic acid solution (10%, 1 mL). The mixture was worked up as usual to give the title compound (2.06 g, 90% yield). Oil; TLC (EtOAc/hexane (1:9)) R_f = 0.21; IR (neat) 3439, 3057, 2963, 2233, 1041 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.13 (1H, s), 3.85 (4H, s), 7.29-7.32 (3H, m), 7.42-7.47 (2H, m); MS *m/z* (rel intensity) 228 (5, M^+), 211 (1), 179 (100), 115 (80), 77 (30); HRMS calcd for $C_{11}H_{10}{}^{35}Cl_2O$ (M^+) 228.0109; found *m/z* 228.0107.

1,3-Dichloro-2-(2,4-difluorophenyl)-2-propanol (2d)[5a,c]

A sample of $CeCl_3 \cdot 7\,H_2O$ (2.44 g, 6.53 mmol) was dried at 140 °C *in vacuo* for at least 3 h, and then cooled under an argon atmosphere. Anhydrous THF (32.5 mL) was added, and the suspension was stirred for at least 4 h before use. Under an atmosphere of argon, a solution of 1-bromo-2,4-difluorobenzene (1.21 g, 6.0 mmol) in THF (5 mL) was stirred at -78 °C, and butyllithium (7.5 mmol, 4.9 mL of 1.6 M solution in hexane) was added dropwise over a period of 10 min. After the addition was completed, the dark solution was stirred for 20 min, and then transferred via a Teflon tube under a pressure of nitrogen to the prepared suspension of cerium trichloride (6.53 mmol) in THF at -78 °C. The mixture was stirred at -78 °C for 1 h, and a solution of 1,3-dichloroacetone (0.61 g, 4.81 mmol) in THF (3 mL) was added in one portion. After which the mixture was stirred for 15 min, and quenched by addition of aqueous acetic acid (10%, 1 mL). The mixture was diluted with brine (15 mL), and extracted with ethyl acetate (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated by rotary evaporation, and the residue was purified on a silica gel column by elution with EtOAc/hexane (3:97) to give the title compound (1.11 g, 96% yield based on 1,3-dichloroacetone). Oil; TLC (EtOAc/hexane (3:97)) R_f = 0.27; IR (neat) 3580 (br), 1568, 1458, 1340, 1215, 988, 878, 707 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.67-3.77 (1H, OH), 3.96 (2H, d, *J* = 11.3 Hz), 4.10 (2H, d, *J* = 11.3 Hz), 6.79-7.57 (3H, m).

Fluconazole (3)[4]

A mixture of 1,2,4-triazole (602 mg, 8.7 mmol) and potassium carbonate (1.2 g, 8.7 mmol) in DMF (25 mL) was heated at reflux for 1 h under a nitrogen atmosphere. A solution of 1,3-dichloro-2-(2,4-difluorophenyl)-2-propanol (**2d**, 1.0 g, 4.0 mmol) in DMF (5 mL) was added dropwise. The mixture was heated at reflux for 16 h and cooled. Water (100 mL) was added, and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed on a silica gel column by elution with MeOH/CH_2Cl_2 (5:95) to give the title compound. Recrystallization from EtOAc/hexane gave white solids (890 mg, 70% yield), mp 138.5-140 °C (lit.[4] mp 138-140 °C).

TLC (MeOH/CH_2Cl_2 (5:95)) R_f = 0.23; IR (KBr) 3126, 1618, 1503, 1422, 1278, 1140, 967, 678 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.43 (2H, d, *J* = 14.3 Hz), 4.72 (2H, d, *J* = 14.3 Hz), 5.51 (1H, s), 6.68-6.82 (2H, m), 7.34-7.44 (1H, m), 7.81 (2H, s), 8.02 (2H, s); ^1H NMR (acetone-d_6, 200 MHz) δ 4.65 (2H, d, *J* = 14.3 Hz), 4.95 (2H, d, *J* = 14.3 Hz), 6.85-6.90 (2H, m), 7.26-7.37 (1H, m), 7.80 (2H, s), 8.35 (2H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 54.8, 54.9, 75.3, 103.9, 104.3, 104.6, 112.0, 112.3, 130.1, 144.6, 151.9. Anal. Calcd. for $C_{13}H_{12}F_2N_6O$: C, 50.98; H, 3.95; N, 27.44. Found: C, 51.20; H, 4.10; N, 27.07.

2-Chloromethyl-2-phenyloxirane (4a)[3b]

A mixture of 1,3-dichloro-2-phenyl-2-propanol (**2a**, 385 mg, 1.8 mmol) and *t*-BuOK (430 mg, 3.6 mmol) in *t*-BuOH (10 mL) was stirred at room temperature for 30 min. After removal of solvent under reduced pressure, the residue was taken up with EtOAc (20 mL) and washed with brine (2 × 5 mL). The organic phase was dried (Na_2SO_4), concentrated, and chromatographed on a silica gel column by elution with EtOAc/hexane (5:95) to give the title compound (278 mg, 92%). Oil; TLC (EtOAc/hexane 5:95)) R_f = 0.25; IR (neat) 3061, 2992, 1254, 1071 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.90 (1H, d, *J* = 5.2 Hz), 3.18 (1H, d, *J* = 5.2 Hz), 3.80 (1H, d, *J* = 12.0 Hz), 4.07 (1H, d, *J* = 12.0 Hz), 7.32-7.45 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 47.8, 55.1, 59.1, 126.1, 128.0 (2 ×), 128.3 (2 ×), 136.5; MS *m/z* (rel intensity) 168 (7, M^+), 133 (40), 104 (100); HRMS calcd for C_9H_9ClO (M^+) 168.0341; found *m/z* 168.0347.

2-Chloromethyl-2-(phenylethynyl)oxirane (4c)

The reaction of 1-chloro-2-(chloromethyl)-4-phenyl-3-butyn-2-ol (**2c**, 684 mg, 3 mmol) with *t*-BuOK (672 mg, 6 mmol) in *t*-BuOH, by a procedure similar to that for **4a**, gave oxirane **4c** (530 mg) in 90% yield. Oil; TLC (EtOAc/hexane (1:99)) R_f = 0.14; IR (neat) 3058, 2236, 1488 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.03 (1H, d, *J* = 5.3 Hz), 3.18 (1H, d, *J* = 5.3 Hz), 3.72 (2H, s), 7.28-7.30 (3H, m), 7.44-7.46 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.2, 50.3, 54.1, 84.3 (2 ×), 121.2, 128.1 (2 ×), 128.8 (2 ×), 131.7; MS *m/z* (rel intensity)

192 (25, M^+), 162 (35), 127 (100); HRMS calcd for $C_{11}H_9{}^{35}ClO$ (M^+) 192.0341; found *m/z* 192.0331.

3-Chloro-2-phenyl-1,2-propanediol (5a)[6c]

A solution of 2-chloromethyl-2-phenyloxirane (**4a**, 204 mg, 1.9 mmol) and concentrated H_2SO_4 (0.5 mL) in CH_3CN (20 mL)/water (10 mL) was heated at reflux for 2 h. After removal of CH_3CN under reduced pressure, the residue was extracted with EtOAc (2 × 10 mL). The organic phase was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and chromatographed on a silica gel column by elution with EtOAc/hexane (3:7) to give diol **5a** (148 mg, 80%). Oil; TLC (EtOAc/hexane (3:7)) R_f = 0.12; IR (neat) 3355, 2929, 1444, 1044, 763 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.72 (1H, br s), 3.38 (1H, br s), 3.78 (1H, br s), 3.79 (1H, br s), 3.87 (1H, d, *J* = 11.4 Hz), 3.95 (1H, d, *J* = 11.4 Hz), 7.30-7.46 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 50.6, 67.7, 76.3, 125.4, 127.9 (2 ×), 128.4 (2 ×), 140.5; MS *m/z* (rel intensity) 186 (1, M^+), 155 (100); HRMS calcd for $C_9H_{11}{}^{35}ClO_2$ (M^+) 186.0447, found *m/z* 186.0440.

3-Chloromethyl-4-phenylbut-3-yne-1,2-diol (5c)[6c]

Treatment of 2-chloromethyl-2-(phenylethynyl)oxirane (**4c**, 192 mg, 1 mmol) with catalytic amount of concentrated H_2SO_4, by a procedure similar to that for **5a**, gave diol **5c** (189 mg, 90%). Solid, mp 136-137 °C; TLC (EtOAc/hexane (3:7)) R_f = 0.15; IR (KBr) 3271, 2234, 1483, 1117, 1017 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.12 (1H, br s), 2.97 (1H, br s), 3.77-3.90 (4H, m), 7.27-7.34 (3H, m), 7.42-7.45 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.7, 67.0, 71.5, 86.5, 86.7, 121.5, 128.3 (2 ×), 129.0 (2 ×), 131.9; MS *m/z* (rel intensity) 210 (5, M^+), 179 (100); HRMS calcd for $C_{11}H_{11}{}^{35}ClO$ (M^+) 210.0447, found 210.0448.

2-Hydroxymethyl-2-phenyloxirane (6a)[6c]

A mixture of 3-chloro-2-phenyl-1,2-propanediol (**5a**, 185 mg, 1 mmol) and K_2CO_3 (1.4 mg) was stirred in MeOH (6 mL) at room temperature for 8 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on a silica gel column by elution with EtOAc/hexane (2:8) to give glycidol **6a** (130 mg, 90%). Oil; TLC (EtOAc/hexane (2:8)) R_f = 0.18; IR (neat) 3389, 3058, 1491, 1440, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.20 (1H, br s), 2.82 (1H, d, *J* = 5.3 Hz), 3.27 (1H, d, *J* = 5.3 Hz), 3.99 (1H, dd, *J* = 12.5, 8.6 Hz), 4.10 (1H, dd, *J* = 12.5, 3.8 Hz), 7.28-7.40 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 52.4, 60.4, 63.0, 125.9, 128.0 (2 ×), 128.4 (2 ×), 137.0; MS *m/z* (rel intensity) 150 (10, M^+), 133 (75), 91 (100); HRMS calcd for $C_9H_{10}O_2$ (M^+) 150.0680, found *m/z* 450.0676.

ACKNOWLEDGMENT

We thank the National Science Council for financial support.

Received December 4, 2002.

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