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Facile and Efficient Synthesis of (*R*)-4-(Benzyloxy)-3-methylbutanenitrile: Toward Developing a Versatile Chiral Building Block

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A practical synthesis of (*R*)-4-(benzyloxy)-3-methylbutanenitrile, a potential chiral building block, from the corresponding *α*-keto ester in high yield and large scale was presented.

Keywords synthetic methods, rearrangement, (*R*)-4-(benzyloxy)-3-methylbutanenitrile, chiral building block

Introduction

Chiral methyl units widely exist in many natural products and pharmaceutical compounds, and chiral pool strategy is one of the best options for introducing such units. The access to suitable chiral building blocks (natural or unnatural) is therefore of great interest. The variety of terpenes (citronellal, menthol, pulegone *etc*., Figure 1) are great but their utilization is greatly limited for the lack of flexibility.[1] Commercial Roche esters are versatile but expensive, hence, cheaper succedaneum and derivatives are still in demand.

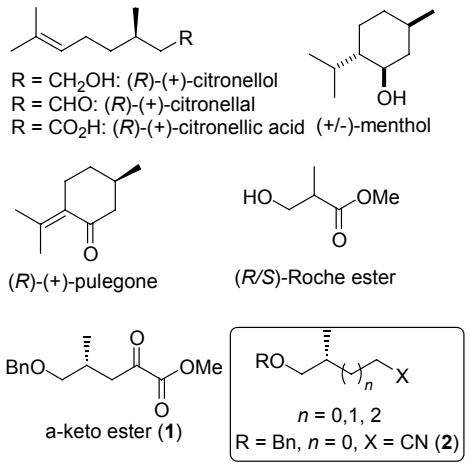

Figure 1 Selected chiral methyl building blocks.

As a part of our project to exclude CrO_3 from the degradation of steroidal sapogenins, we have developed a green oxidation process which also enabled the access of (*R*)-methyl 5-(benzyloxy)-4-methyl-2-oxopentanoate (**1**) in kilogram scale.[2] The functionalities of **1** offered us unique opportunity to develop a series of chiral building blocks. Herein, we set (*R*)-4-(benzyloxy)-3-methyl-butanenitrile (**2**)[3] as our primary target because the versatility and stability of CN group make it an excellent candidate as a chiral building block.

Experimental

(*R*)-Methyl 5-(benzyloxy)-2-(hydroxyimino)-4-methylpentanoate (3)

To a solution of *α*-keto ester (**1**, 100 g, 0.40 mol) in EtOH (400 mL) was added NH_2OH•HCl (34.5 g, 0.50 mol, 1.25 equiv.) and NaOAc (41.0 g, 0.50 mol, 1.25 equiv.). The resulting mixture was warmed to reflux for 4 h and quenched with water (600 mL). The mixture was extracted with ethyl acetate (300 mL×4), and the combined organic phase was washed with brine, dried over Na_2SO_4. Concentration under reduced pressure afforded crude **3** (106 g, quantitative yield) as colorless liquid which was used in next step without further purification. R_f=0.40 (silica gel, EtOAc∶hexane, 1∶4); $[\alpha]_D^{27}$ −15.5 (*c* 1.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.36—7.29 (m, 4H), 7.29—7.23 (m, 1H), 4.46 (s, 2H), 3.75 (s, 3H), 3.41—3.27 (m, 2H), 2.71 (dd, *J*=12.8, 7.4 Hz, 1H), 2.60 (dd, *J*=12.8, 7.2 Hz, 1H), 2.32 (dq, *J*=13.5, 6.8 Hz, 1H), 0.96 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 164.27, 151.99, 138.49, 128.29 (2C), 127.53 (2C), 127.44, 75.75, 72.85, 52.49, 31.63, 29.47, 17.36; IR (KBr) *v*: 3277, 3031, 2956, 2930,

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2872, 1728, 1630, 1214, 1151, 736 cm^{-1}; MS (ESI) *m/z*: 288.2 ($[M+Na]^+$); HRMS (ESI) calcd for $C_{14}H_{19}NONa^+$ 288.1206, found 288.1213.

(*R*)-Methyl 5-(benzyloxy)-4-methyl-2-(((methylsulfonyl)-oxy)imino)pentanoate (5)

To a well-stirred solution of crude **3** (0.40 mol) in dry CH_2Cl_2/Et_3N (400 mL/220 mL) was added MsCl (55 g, 0.48 mol, 1.2 equiv.) under a ice-water bath. After stirring for 90 min at room temperature, the mixture was quenched by adding water (500 mL). The resulting biphasic system was separated and the aqueous phase was extracted with CH_2Cl_2 (300 mL×3), and the combined organic phase was washed with brine, dried over Na_2SO_4. Concentration under reduced pressure afforded crude **5** (136.4 g) as a dark red liquid which was used in next step without further purification. Analytic sample was obtained after flash column chromatography on silica gel. R_f=0.8 (silica gel, EtOAc∶hexane: 1∶4); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.34—7.24 (m, 5H), 4.41 (d, J=1.7 Hz, 2H), 3.72 (s, 3H), 3.39 (dd, J=9.3, 4.6 Hz, 1H), 3.24 (t, J=8.9 Hz, 1H), 3.14 (s, 3H), 2.76 (dd, J=12.8, 8.5 Hz, 1H), 2.68 (dd, J=12.8, 6.2 Hz, 1H), 2.34—2.22 (m, 1H), 0.96 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.64, 160.77, 138.15, 128.37 (2C), 127.61, 127.56 (2C), 75.35, 72.92, 53.13, 36.81, 32.43, 32.15, 17.28; IR (KBr) *v*: 3030, 2958, 2937, 2859, 1735, 1623, 1217, 1186, 1096, 523 cm^{-1}; MS (ESI) *m/z*: 365.9 ($[M+Na]^+$); HRMS (MALDI) calcd for $C_{15}H_{21}NO_6SNa^+$ 366.0994, found 366.0982.

(*R*)-4-(Benzyloxy)-3-methylbutanenitrile (2)

To a well-stirred solution of sodium methoxide (22.6 g, 0.42 mol, 1.05 equiv.) in MeOH (400 mL) was added crude **5** dropwise at −10 ℃ (ice/EtOH bath). A white deposition (MsONa) was formed and the reaction completed after 90 min. The mixture was filtered and washed with ethyl acetate, and then the filtrate was concentrated and diluted with water (200 mL). The resulting mixture was extracted with ethyl acetate (300 mL×4), and the combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated. Distillation under reduced pressure (141 ℃, 8 mmHg) gave nitrile **2** (63.2 g, 84%, 98.5% *ee* by HPLC analysis) as a colorless liquid. R_f=0.8 (silica gel, EtOAc∶hexane: 1∶5); b.p. 282 ℃; $[\alpha]_D^{28}$ +30.3 (*c* 1.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.39—7.27 (m, 5H), 4.52 (s, 2H), 3.47 (dd, J=9.4, 4.7 Hz, 1H), 3.31 (dd, J=9.2, 8.0 Hz, 1H), 2.51 (dd, J=16.7, 5.3 Hz, 1H), 2.39 (dd, J=16.7, 7.0 Hz, 1H), 2.24—2.11 (m, 1H), 1.09 (d, J=6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.14, 128.50, 128.37, 127.92, 127.79, 127.66, 118.75, 73.24, 31.14, 21.37, 16.26; IR (film) *v*: 3088, 3031, 2964, 2929, 2860, 2245, 1731, 1604, 1206, 739 cm^{-1}; MS (ESI) *m/z*: 212.1 ($[M+Na]^+$). Anal. calcd for $C_{12}H_{15}NO$: C 76.2, H 7.94, N 7.41; found C 76.00, H 8.09, N 7.32; HPLC (chiral) Chiralpak AS-H at 23 ℃, λ = 214 nm, hexane∶isopropanol: 98∶2, retention times 19.6 min (*R*), 21.3 min (*S*) at 0.7 mL/min flow rate. The racemic nitrile **2** was synthesized from 2-methylpropane-1,3-diol according the procedure described in reference [3].

Results and Discussion

Beckmann-type reaction was hence chosen to cleave C(1)—C(2) bond (Scheme 1, type II, Beckmann fragmentation).[4] Ketoxime **3** was easily prepared by treating α-keto ester with NH_2OH•HCl in ethanol and several typical conditions of Beckmann reaction were examined thereafter (Table 1). As expected, treatment of ketoxime **3** in acidic medium generated nitrile **2** as the only identifiable compound in moderate yield (Table 1, Entries 1—3).

Scheme 1 Transformations of ketoxime **3**

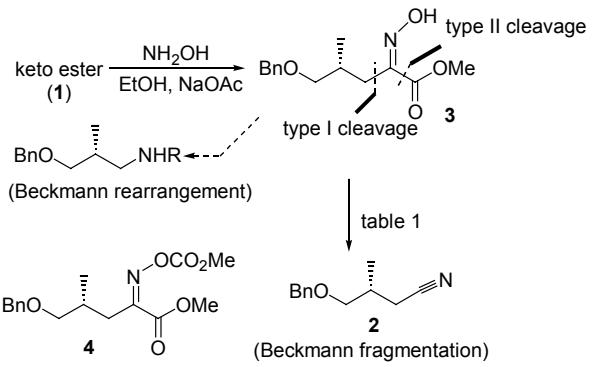

Table 1 Conditions for transforming ketoxime **3** into nitrile **2**

Entry	Condition	Results[a]
1	$SOCl_2$ or $POCl_3$, CH_2Cl_2, RT to reflux, 5 h	Complex
2	Ac_2O, 4 mol/L HCl, EtOH, reflux, 6 h	64% **2**
3	12 mol/L HCl, MeOH, reflux, 5 h	55% **2**
4	$C_4F_9SO_2F$, DBU, CH_2Cl_2, 0 ℃, 30 min	45% **2**+41% **4**

[a] Isolated yield.

The reaction condition was further screened and the balance of mass was finally realized when **3** was treated with $C_4F_9SO_2F$ in the presence of DBU in dry CH_2Cl_2 at 0 ℃, providing nitrile **2** and methyl carbonate **4** in comparable yield (Entry 4). The generation of **4** indicated that an external nucleophilic attack at ester group [C(1)] might greatly facilitate the decarboxylation and the cleavage of N—O bond during the reaction, hence provided us definite clue for further optimization.

As outlined in Scheme 2, ketoxime **3** was transformed into stable methanesulfonate **5**, and the latter was treated with stoichiometric amount of sodium methoxide in dry methanol under an ice-ethanol bath for 90 min to furnish the desired nitrile **2** smoothly in excellent yield (84%—86% from α-keto ester **1**) and high enantiomeric excess (98.5% for every batch, inherited from **1**). Although the scope of this reaction was not expanded yet, the effectiveness and robustness of our procedure were tested by running the reaction at 100 g

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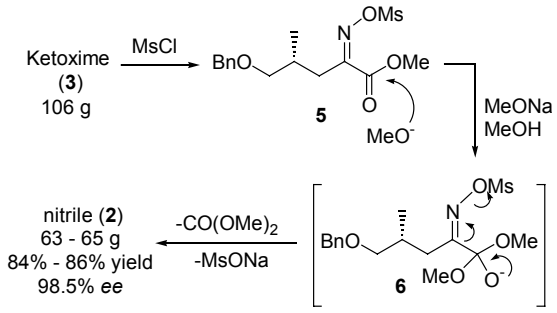
Scheme 2 Synthesis of nitrile **2**



scale for three times.

Conclusions

We have developed a mild method for nitrile synthesis from α-ketoester, by which we prepared (*R*)-4-(benzyloxy)-3-methylbutanenitrile in large scale. The ease of manipulation will make nitrile **2** a competitive reagent for synthetic chemists. Currently, derivation and commercialization of ketoester **1** and nitrile **2** are ongoing in our laboratory.

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