Synthesis of 1-(2-Methoxybenzyl)-1,10-phenanthroline-1-ium Bromide from the Gandapura Oil

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ABSTRACT

This study describes a simple synthetic method to prepare 1-(2-methoxybenzyl)-1,10-phenanthroline-1-ium bromide from gandapura oil. The salt was synthesized in four steps. Initially, commercial gandapura oil was directly subjected to the alkylation reaction under basic condition using dimethyl sulfate to give methyl 2-methoxybenzoate in 86% yield. Next, the produced benzoate ester was reduced by LiAlH4 to produce 2-methoxybenzyl alcohol in 67% yield. The treatment of benzyl alcohol with phosphorus tribromide under solvent free condition produced the corresponding benzyl bromide (in 67% yield), which was directly introduced into bimolecular nucleophilic substitution reaction with 1,10-phenanthroline monohydrate to finally give the desired product in 63% yield.

Keyword: phenanthroline salt, gandapura oil, alkylation, reduction, halogenations, and bimolecular nucleophilic substitution.

INTRODUCTION

Until now, 1,10-phenanthroline has been considered as a versatile scaffold in chemistry. It is well known as a complexing bidentate ligand for various transition metal ions since the two nitrogen atoms may act as Lewis base or nucleophile. Due to the remarkable complexing property, this compound has been widely applied in various fields. For the analytical application, it has been utilized in the analysis of metal ions, such as iron as well as captopril drug [1]. In organic chemistry, the ligand properties of 1,10-phenanthroline and its derivatives are often employed in transition metal-catalyzed-reactions [2]. Another report showed that the complex of platinum-1,10-phenanthroline was used as photosesitizer in the degradation of 4-chlorophenol [3]. Several 1,10-phenanthroline derivatives also displayed good biological activities as antibacterial [4] and antiplasmodium [5,6].

In the connection to the pharmaceutical applications, our group have prepared a small library of 1-(N)-substituted-1,10-phenanthrolineum salts [7–12]. These compounds were then subjected to in vitro and in vivo anti plasmodium assay against two strains of Plasmodium falciparum of FCR3 (resistance to chloroquine) and D10 (sensitive to chloroquine) [12–15]. We found that 1-(N)-benzylated-1,10-phenanthrolineum salts exhibited good activity against the parasite and have high potentials to be further developed.

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Following our previous studies, we would like to prepare new derivative of 1-(N)-benzylated-1,10-phenanthrolinium salts from readily accessible starting materials. From the retrosynthetic point of view, 1-(N)-benzylated-1,10-phenanthrolinium salts could be obtained from 1,10-phenanthroline and benzyl halide derivatives via nucleophilic substitution reaction. While the former is commercially available, the latter could be prepared from the corresponding benzyl alcohols. From the screening of natural products, we found that gandapura oil could be good precursors for benzyl alcohols. Gandapura oil, whose, the major component is methyl salycilate (up to 98%) is, however, mainly used as massage oil. In addition, the application of this essential oil as the precursor in the synthesis of phenantroline salt has not been reported yet and may also increase the value of gandapura oil. Therefore, we would like to utilize gandapura oil to synthesize 1,10-phenanthrolinium salt, namely 1-(2-methoxybenzyl)-1,10-phenanthroline-1-ium bromide by using simple synthetic steps.

EXPERIMENT

Chemicals and instrumentation

The materials for this study included gandapura oil (Tekun Jaya, Yogyakarta), 1,10-phenanthroline monohydrate, dimethyl sulfate, 1 M solution of LiAlH₄ in THF, PBr₃, K₂CO₃, NaOH, NaCl, Na₂SO₄, acetone, petroleum ether, ethyl acetate, chloroform and tetrahydrofuran. The materials were purchased from E. Merck and Sigma Aldrich. Column chromatography was carried out on Kieselgel 60 (0.035-0.07 mm) silica gel (Acros Organic).

The instrumentations employed in this study were 1H-NMR spectrometer (Bruker AC400 MHz and 500 MHz JEOL JNM-ECA), GC-MS GC-MS spectrometer (Shimadzu QP-2010), FTIR spectrophotometer (Shimadzu-Prestige 21) and melting-point apparatus (Electrothermal 9100).

Procedure reaction

Synthesis of methyl 2-methoxybenzoate 2

Gandapura oil 1 (methyl salicylate 98%, 1 equiv., 45 mmol, 5.8 mL), acetone (90 mL), potassium carbonate (2 equiv., 90 mmol, 12.43 g) were respectively introduced to a 100 mL of three-necked flask. Dimethyl sulfate (4 equiv., 180 mmol, 17 mL) was added dropwise to reaction mixture at 0 °C. Water was then added to the cooled reaction mixture to dissolve the precipitate. The product was extracted with chloroform for three times. The combined organic layers were washed with water, brine, dried over Na₂SO₄ and evaporated under reduced pressure. The crude product was purified using column chromatography with eluent of (petroleum ether: ethyl acetate = 8:2). Colourless oil; isolated yield: 86%; 1H-NMR (400 MHz, CDCl₃, ppm): δ 7.77-7.80 (HAr, m, 1H), 7.43-7.45 (HAr, m, 1H), 6.96-6.99 (HAr, m, 2H), 3.88 (CH₃, s, 3H), 3.89 (CH₃, s, 3H); FTIR (neat) vₚₕₚₖ: 2970 1675, 1611 1594, 1330, 1183; GC-MS (EI): m/z (%): 166 [M⁺], 135 (base peak), 133, 105, 92, 77, 63.

Synthesis of 2-methoxybenzyl alcohol 3

Solution of methyl 2-methoxybenzoate 2 (1 equiv., 5.2 mmol, 0.86 g) in anhydrous THF (13 mL) was added dropwise to a 1 M solution of LiAlH₄ in THF (2.4 equiv., 12.5 mmol, 12.5 mL) at 0 °C under argon atmosphere. The reaction mixture was stirred overnight at rt. Ethyl acetate was slowly added to the reaction mixture at 0 °C followed with the addition of aqueous solution of NaOH (0.25 M, 2 mL). The mixture was filtered through a pad of celite and washed with ethyl acetate. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried with MgSO₄ and concentrated.
under reduced pressure. The crude product was purified using column chromatography with eluent of (petroleum ether: ethyl acetate = 7:3).

Brownish oil; isolated yield: 67%; $^1$H-NMR (400 MHz, CDCl$_3$, ppm) $\delta$ 7.27-7.30 (H$_{Ar}$, m, 2H), 6.90-7.03 (H$_{Ar}$, m, 2H), 4.70 (CH$_2$, d, $J = 6.0$ Hz, 2H), 3.88 (CH$_3$, s, 3H); FTIR (neat) $\nu_{max}$: 3332, 2978, 1597, 1519, 1234; GC-MS (EI): m/z (%): 138 [M$^+$, base peak], 121, 105, 91, 77, 65.

**Synthesis of 2-methoxybenzyl bromide 4**

Benzyl alcohol derivatives 3 (1 equiv., 10 mmol) were placed in a 100 mL of three-necked flask equipped with condenser and dropping funnel. Phosphorus tribromide (1 equiv., 10 mmol, 0.95 mL) was added dropwise at 0 °C. The mixture was then stirred for 30 min in an ice bath and at room temperature for 1 h. The reaction was then refluxed for 3 h. Next, cold water (15 mL) was added to the reaction mixture. The mixture was then extracted with chloroform for three times. The organic layer was dried over Na$_2$SO$_4$ anhydrous and evaporated under reduced pressure to give the benzyl bromide derivatives 4 which were directly used in the next step without further purification.

Dark brown oil; isolated yield: 67%; GC-MS (EI): m/z (%): 245 [M$^+$], 165, 137 (base peak), 122, 107.

**Synthesis of 1-(2-methoxybenzyl)-1,10-phenanthroline-1-ium bromide 5**

Benzyl bromide derivatives 4 (1 mmol) and 1,10-phenanthroline monohydrate (1 equiv., 1 mmol, 0.2 g), and 15 mL acetone were introduced to a 100 mL of three-necked flask. The mixture was refluxed for 12 h and then cooled to room temperature. The precipitate was then washed with acetone to yield 1-(2-methoxybenzyl)-1,10-phenanthroline-1-ium bromide. Light red solid; isolated yield: 63%; mp: 199-200°C; $^1$H-NMR (400 MHz, DMSO-d$_6$, ppm): $\delta$: 9.67 (H$_{Ar}$, d, $J = 5.9$ Hz, 1H), 9.50 (H$_{Ar}$, d, $J = 5.9$ Hz, 1H), 9.08 (H$_{Ar}$, d, $J = 6.5$ Hz, 1H), 8.73 (H$_{Ar}$, d, $J = 6.5$ Hz, 1H), 8.50 (H$_{Ar}$, d, $J = 5.9$ Hz, 1H), 8.41-8.42 (H$_{Ar}$, m, 2H), 7.93-7.95 (H$_{Ar}$, m, 1H), 7.27 (CH$_2$, s, 2H), 7.22 (H$_{Ar}$, t, $J = 7.2$ Hz, 1H), 7.05 (H$_{Ar}$, d, $J = 7.2$ Hz, 1H), 6.72 (H$_{Ar}$, t, $J = 7.2$ Hz, 1H), 6.66 (H$_{Ar}$, d, $J = 7.2$ Hz, 1H), 3.79 (CH$_3$, s, 3H); FTIR (KBr) $\nu_{max}$: 3039, 2970, 1597, 1512, 1427, 1249.

**RESULT AND DISCUSSION**

In this report, we have prepared 1-(2-methoxybenzyl)-1,10-phenanthroline-1-ium bromide from readily available starting materials via simple synthetic methods. The new compound may contribute to the construction of our small library of 1-(N)-substituted-1,10-phenanthroline salts [7–12] and were expected to have biological activities. From a synthetic point of view, 1-(2-methoxybenzyl)-1,10-phenanthroline-1-ium bromide can be simply disconnected to give benzyl halides and 1,10-phenanthroline via bimolecular nucleophilic substitution. While the latter is commercially available, the former may be obtained from benzyl alcohols.

Our group is interested in the application of abundance natural products in the synthesis of valuable products. Therefore, we screened natural products which could be precursors for benzyl alcohols. We found that gandapura oil could be potential source for benzyl alcohol. The major component of gandapura oil is methyl salicylate (96-98%), where the benzoate ester could be reduced into the corresponding benzyl alcohol. For these reasons, gandapura oil was chosen as starting materials for the synthesis of 1-(N)-benzylated-1,10-phenanthroline salts.
Figure 1. Synthetic pathway to access 1-(2-methoxybenzyl)-1,10-phenanthroline-1-ium bromide

For the synthetic process (Figure 1), commercial gandapura oil was directly utilized as the source of methyl salicylate 1 (90% of methyl salicylate based on GCMS). Before performing the reduction reaction, methyl salicylate 1 was initially protected since the ester group will be reduced by hydride reducing agent in the next step. The protection was carried out using dimethyl sulfate in basic condition to give methyl 2-methoxybenzoate 2 in 86% yield. The reduction of the protected ester 2 was carried out using strong reducing agent of LiAlH₄ in dry THF and the benzyl alcohol 3 was obtained in 67% yield.

Before introducing benzyl group into 1,10-phenantroline unit, the produced benzyl alcohol 3 should be activated. In this context, the alcohol 3 was transformed into the corresponding benzyl bromide. The bromination of the key intermediate 3 was performed using phosphorus tribromide to afford 2-methoxybenzyl bromide 4 (in 67% yield) possessing bromide as a good leaving group. It should be noted that the bromination reaction was successfully carried out under solvent free condition, which is in a good agreement with Green Chemistry Principles. The benzyl bromides 4 were directly subjected into bimolecular nucleophilic substitution using 1,10-phenanthroline as nucleophile [5]. To our delight, the desired products of 1-(2-methoxybenzyl)-1,10-phenanthroline-1-ium bromide 5 as a light red solid with melting point of 199-200 °C in 63% yield (Figure 1).

The formation of the products 7 and 8 was confirmed by NMR spectrometer. The presence of all protons from phenanthroline and aryl skeletons together with the characteristic protons around 7.20-7.30 ppm representing the protons at benzylic position adjacent to positively-charged-nitrogen of phenanthroline indicated that 1-(2-methoxybenzyl)-1,10-phenanthroline-1-ium bromide 5 has been generated [16]. The new product 5 contributed to our small library of 1-(N)-benzyl-substituted-1,10-phenanthroline-1-ium salts.

CONCLUSION

The salt of 1-(2-methoxybenzyl)-1,10-phenanthroline-1-ium bromide have been prepared starting from readily available Gandapura oil in good yields. The salts were synthesized from wintergreen oil (methyl salicylate) and vanillin in four steps comprising alkylation, reduction, halogenation and bimolecular nucleophilic substitution reactions.

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CONFLICT OF INTEREST

Authors declare no competing interest.
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