An Improved Produce for the Synthesis of 4-Benzyloxy-3-nitro-α-bromoacetophenone

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ABSTRACT: OBJECTIVE To synthesize 4-benzyloxy-3-nitro-α-bromoacetophenone. **METHODS** 4-benzyloxy-3-nitro-α-bromoacetophenone was synthesized in three steps starting from p-hydroxyacetophenone including nitration, benzylation, bromization, with overall yield of 45.2%. **RESULTS** The melting point and IR, ^{1}HNMR of the product were identical with that of the reported one. **CONCLUSION** The process can be easily controlled and is suitable for a scale production.

KEY WORDS: 4-benzyloxy-3-nitro-α-bromoacetophenone; formoterol; synthesis

4-苄氧基-3-硝基-α-溴代苯乙酮的合成工艺改进

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摘要:目的 合成4-苄氧基-3-硝基-α-溴代苯乙酮,并进行工艺改进。**方法** 以对羟基苯乙酮为原料,经过硝化、苄基化、溴代三步反应合成得到4-苄氧基-3-硝基-α-溴代苯乙酮,总收率达到45.2%。**结果** 合成产物经熔点、红外光谱、核磁共振谱等分析确定结构正确;与文献报道一致。**结论** 与其他文献方法比较,该法具有操作简单、收率高、污染小、成本低等特点,并可用于工业生产。

关键词:4-苄氧基-3-硝基-α-溴代苯乙酮;福莫特罗;合成

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4-Benzyloxy-3-nitro-α-bromoacetophenone **1** is an important intermediate for the synthesis of formoterol, a long acting β_2-agonist used as a bronchodilator in the therapy of asthma and chronic bronchitis[1]. The synthesis of **1** was described in earlier literatures.[2-3] Starting from p-hydroxyacetophenone **2**, **1** was synthesized in three steps, including nitration, benzylation, bromization. However, these procedures

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are neither practical nor efficient. First, fuming nitric acid is a strong causticity material, easy to vaporize and difficult to produce in the industry. Second, benzylation needed too long time. Third, bromine was toxic, easy to decay and with strong volatility and serious pollution to the environment. In order to resolve these problems, nitric acid and acetic acid were applied as nitrating agents, which made the procedure simple with carefully operation to avoid the explosion of the nitration reagent. Besides, under TLC analysis and contrast with the reaction reported in literature[2], tetra butyl ammonium bromide was used as a phase transfer catalyst to reduce the reaction time and increase the yield. Finally bromine was replaced with cupric bromide to render the whole procedure convenient and safety. This system is the cleanest and the most direct selective bromination reported to date. The synthesis of **1** was outlined in Fig 1.

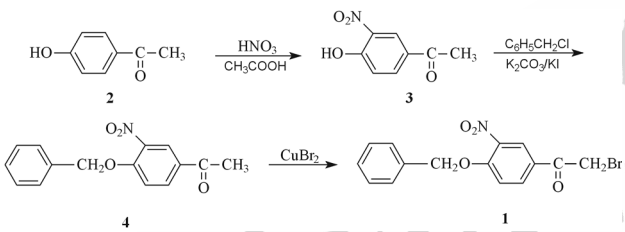

Fig 1 Synthesis of 4-benzyloxy-3-nitro-α-bromoacetophenone

图 1 4-苄氧基-3-硝基-α-溴代苯乙酮的合成

1 Experimental

Melting points were measured with a Beijing Taike X-4 Melting Point microscope apparatus and uncorrected. ^{1}HNMR spectra was recorded on a Bruker AC-P300; IR spectra was recorded on a Bruker-Tensor27 spectrometer. Other reagents employed were of analytical grade and commercially available.

1.1 4-hydroxy-3-nitroacetophenone (**3**)

A solution of nitric acid (65% – 68%, 5.6 mL, 0.13 mol) was added dropwise to a stirred solution of p-hydroxyaceto-phenone **2** (15.0 g, 0.11 mol) in acetic acid (56 mL). The reaction mixture was refluxed for 2 h in water bath at 43 – 50 ℃, and then cooled to room temperature. A yellow precipitate which was collected with suction, was washed with ice water and **3** was obtained. (12.3 g, 62 %). m.p. 131-132 ℃ (recrystallized from ethanol). (lit.[4]: 47%, 132 – 132.5 ℃)

1.2 4-benzyloxy-3-nitroacetophenone (**4**)

A 500 mL three-neck flask was charged with compound **3** (20 g, 0.11 mol), potassium iodide (3.5 g, 0.02 mol), tetra butyl ammonium bromide (6.4 g, 0.02 mol), anhydrous potassium carbonate (38 g, 0.28 mol), water (100 mL) and chloroform (100 mL). Benzyl chlorid (13.84 mL, 0.12 mol) was added slowly dropwise. After addition, the solution was refluxed for 3 h. Then the organic phase was separated quickly. The water phase was then extracted with chloroform (15 mL × 2). The extracts were combined and evaporated under reduced pressure, leading to a yellow precipitate **4** (36.8 g, 90 %). m.p. 134 – 136 ℃ (recrystallized from acetone). (lit.[5]: 80%, 135.5 – 137 ℃)

1.3 4-benzyloxy-3-nitro-α-bromoacetophenone (**1**)

A 100 mL three-neck flask was charged with compound **4** (3.30 g, 0.012 5 mol), cupric bromide (5.47 g, 0.024 5 mol), ethyl acetate (36 mL) and chloroform (36 mL). The reaction mixture was refluxed 1.5 h, then suction quickly. The precipitate was washed with ethyl acetate. The organic phase was washed with water to pH 7 and successively separated, dried over anhydrous $MgSO_4$ and evaporated to give a pale yellow precipitate **1** (3.51 g, 80%). m.p. 135 – 137 ℃ (recrystallized from ethanol). ^{1}H-NMR ($CDCl_3$) δ: 4.376 (s, 2H, $-CH_2Br$), 5.346 (s, 2H, $-CH_2O-$), 7-9 (m, 8H, Ph-H). IR (KBr, cm^{-1}): 2925, 1730, 1697, 1611, 1570, 1530, 1497, 1452, 1348, 1278, 1077, 822, 761, 592. MS m/z: 91, 121, 123, 179, 270.

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