Chinese Chemical Letters Vol. 15, No. 3, pp 288-291
http://www.imm.ac.cn/journal/ccl.html

Synthesis of 1-Bromo-3-methoxy-4-propoxy-5-iodobenzene—A Novel Efficient Process for the Synthesis of Brominated Aromatic Compound

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Abstract: The reaction of aromatic carboxylic acid with oxalyl chloride gives rise to the corresponding acid chloride which without purification is treated with the sodium salt of mercaptopyridine oxide in the presence of 2,2-azo-bisisobutyronitrile (AIBN), radical initiator to give a brominated aromatic compound. After etherification and oxidation, 5-iodovaniline was converted to trisubstituted benzene carboxylic acid which give 1-bromo-3-methoxy-4-propoxy-5-iodobenzene by this new brominating process with a yield of 74 %.

Keyword: Synthesis, radical substitution, 1-bromo-3-methoxy-4-propoxy-5-idiobenzene, bromination.

2, 5-*Trans*-diaryltetrahydrofurans sach as MK-287[1] have been recently identified as competitive antagonists of platelet activating factor(PAF) receptor[1,2]. These compounds could be the good candidates for the therapy of asthma, inflammation, ischemia or acute allergy. For synthesis of MK-287, 1-bromo-3-methoxy-4-propoxy-5-iodoben-zene is an intermediate, which can be synthesized by the Sandmeyer reaction from the corresponding aromatic amine with poor yields. Doyle *et al.* [3] have reported a direct synthetic process from aromatic amine to aromatic halide. But aromatic dibromides were easily given by this method and they were difficultly separated from monobromide. We wish to report in this paper a novel route in which the bromine atom could be introduced by a radical reaction.

Results and Discussion

Iodovanilin **1** was treated in DMF with 1.5 equiv. Of 1-bromopropane in the presence of cesium carbonate to give the *O*-alkylated aldehyde **2** in 96 % yield. The aldehyde **2** was then oxidized with sodium chlorite, following the method of Nilson[4] to give the acid

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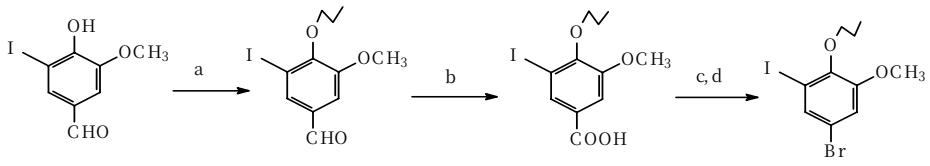
3 with the yield of 91 %. **3** was reacted with oxalyl chloride to give the corresponding acid chloride. Without purification the acid chloride was treated with the sodium salt of mercaptopyridine oxide in bromotrichloromethane in the presence of radical initiator AIBN under Barton conditions[5] (**Scheme 1**). The dihalide **4** thus obtained in 74 % yield.

Scheme 1



1 2 3 4

a: PrBr, $CsCO_3$, DMF,50℃, 2 h; b: NaCl O_2, NaH_2PO_4, *t*-BuOH, 2-methyl-2-butene, 20℃, 4 h;
c: (COCl)$_2$, 20℃, 18 h; d: mercaptopyridine oxide sodium salt, $BrCCl_3$, AIBN, reflux, 2 h;

Experimental

NMR spectra were recorded on a Bruker AM250 spectrometer with tetramethylsilane as an internal standard. Mass spectra were obtained with a GC-MS R.10-10. The thermometer was not corrected. Elemental analysis was performed by the analytical center of Gif/Yvette in France. All reactions were carried out under argon atmosphere and monitored by thin-layer chromatograph (TLC). The data of NMR, IR and elemental analysis of compounds **2**～**4** were listed in **Table 1**.

4-Propyl-5-iodovanillin **2**

To a solution of iodovanilin **1** (2.426 g, 8.72 mmol) in DMF (10 mL) was added in one portion anhydrous cesium carbonate (3.4 g, 10.4 mmol) followed by 1-bromopropane (2 g, 13.1 mmol). The mixture was heated to 50℃ and stirred for 2 h. The mixture was cooled to room temperature and diluted with water (10 mL). The pH of the mixture was adjusted to 6.0 by 2 mol/L HCl, controlling the release rate of carbon dioxide gas carefully. The solution was then extracted with ethyl acetate (3×25 mL). The combined organic phases were washed with brine (10 mL) , drided over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ether, 7/3) to give ether **2** (2.68 g, 96 %).

3-Methoxy-4-propoxy-5-iodo benzoic acid **3**

4-Propyl-5-iodovanillin **2** (2.05 g, 6.4 mmol) and 2-methyl-2-butene (6.4 mL) were dissolved in *tert*-butanol (20 mL) , and a solution of 80 % sodium chlorite (1.45 g, 12.8 mmol) and monobasic sodium phosphate (1.15 g, 8.32 mmol) in water (13 mL) was added dropwise. The mixture was stirred for 4 h at room temperature. The solvent was removed *in vacuo* and the residue was diluted with water (40 mL). The pH of the

solution was adjusted to 10 with 1 mol/L aqueous NaOH, extracted with ether (2×20 mL). The aqueous layer were acidified to pH 2 with 3 mol/L aqueous HCl and extracted with ethyl acetate (3×25 mL) . The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. White crystals of pure acid 3 were obtained (1.97 g, 91 %) , mp = 139～140℃.

To a solution of acid **3** (1.95 g, 5.80 mmol) in CH_2Cl_2 (50 mL) with three drops of DMF was added dropwise oxalyl chloride (950 μL, 11.6 mmol) at room temperature. The mixture was stirred for 18 h. The solvent was removed *in vacuo* and the residue was used directly without purification. To a suspension of mercaptopyridine oxide sodium salt in refluxing bromotrichloromethane (30 mL) was added dropwise (2 h) the solution of the acid chloride and AIBN (150 mg) in the same solvent (30 mL) under argon. The mixture was heated for further 5 min, the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (eluent: petroleum ether/AcOEt, 9/1) to give bromide **4** (1.6 g, 74 %).

Table 1 The data of IR,NMR and elemental analysis for compounds **2～4**

Compound	IR (ν /cm^{-1})	^{1}H NMR (δ ppm,J Hz)	^{13}C NMR (δ ppm)	Elemental analysis % (calculated)	
				C	H
2	2950, 1680, 1575 1550, 1405	1.03 (t, 3H, *J*=7.4), 1.81 (m, 2H), 3.84 (s, 3H), 4.01 (t, 2H, *J*=6.7,), 7.35 (d, 1H, *J*= 1.61), 7.81 (d, 1H, *J*=1.6), 9.78 (s, 1H)	10.7, 23.7, 56.1, 75.3 92.5, 110.9, 133.7, 134.9, 152.8, 153.7, 189.8		
3	3430, 2972, 2935, 2655, 1692, 1589, 1558, 1459, 1422, 1287	1.09 (t, 3H, *J*=7.4), 1.88 (m, 2H), 3.92 (s, 3H), 4.06 (t, 2H *J*=6.7), 7.06 (d, 1H, *J*=1.6), 8.16 (d, 1H, *J*=1.6), 9.0～ 10.0 (s, 1H)	10.6, 23.5, 56.0, 75.1, 92.1, 113.9, 125.9, 133.2, 151.9, 152.9, 170.8	(39.31) 39.35	(3.90) 3.87
4	3081, 2962, 2936, 2876, 1568, 1463, 1441, 1255, 1033	1.06 (t, 3H, *J*=7.4), 1.85 (m, 2H), 3.83 (s, 3H), 3.91 (t, 2H, *J*=6.8), 7.00 (d, 1H, *J*=2.1), 7.49 (d, 1H, *J*=2.0)	10.5, 23.3, 55.9, 74.6, 93.0, 115.9, 116.8, 132.0, 147.5, 152.6	(32.37) 32.37	(3.26) 3.28

1-Bromo-3-methoxy-4-propoxy-5-iodobenzene **4**

Acknowledgments

This research was supported by the Chinese-French Cooperation Commission of Science and Technology, the Science and Technology Commission of Zhejiang Provence.

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Received 15 April, 2003