

Synthesis, Reactivity and Stability of Aryl Halide Protecting Groups towards Di-Substituted Pyridines

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ABSTRACT

This paper reports the synthesis and reactivity of different Benzyl derivative protecting groups. The synthesis and stability of Benzyl halides, 4-methoxybenzyl halides, 3,5-dimethoxybenzyl halides, 3,4-dimethoxybenzyl halides, 3,4,5-trimethoxybenzyl halide protecting groups and their reactivity towards nitrogen atom of a di-substituted pyridine ring in formation of pyridinium salts is also reported.

Keywords: aryl halide protecting groups; benzyl halides; 4-methoxybenzyl halide; 3,5-dimethoxybenzyl halide; 3,4-dimethoxybenzyl halide

ABSTRAK

Naskah ini melaporkan hasil sintesis dan reaktivitas beberapa jenis gugus pelindung turunan benzil. Sintesis dan kestabilan dari benzil halida, 4-metoksibenzil halida, 3,5-dimetoksibenzil halida, 3,4-dimetoksibenzil halida, 3,4,5-trimetoksibenzil halida, masing-masing telah dilaporkan. Selain itu dipaparkan pula kajian reaktivitasnya terhadap perlindungan atom nitrogen pada cincin piridin ter-disubstitusi pada pembentukan garam piridinium.

Kata Kunci: gugus pelindung aril halida; benzil halida; 4-metoksibenzil halida; 3,5-dimetoksibenzil halide; 3,4-dimetoksibenzil halida

INTRODUCTION

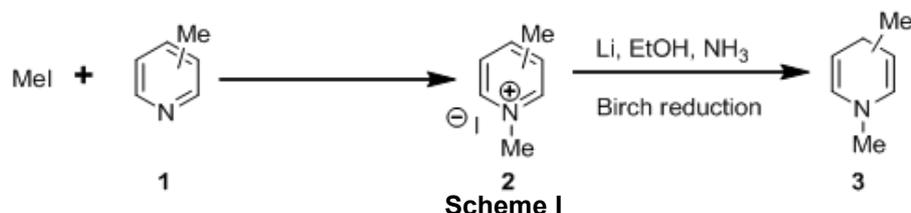
Syntheses of pyridinium salts were first reported by Boesrma in 1980s where *N*-methylpyridinium iodide salts for Birch reductions were prepared [1]. The synthesis started with reactions of *mono*-methyl substituted pyridine **1** with methyl iodide which resulted in formation of the pyridinium salt **2** (**Scheme I**).

Donohoe have also reported extensive work in preparation of *mono*-substituted and *di*-substituted pyridinium salts used in Birch reductions and Ammonia-free Birch reductions [2-5]. For example Donohoe have investigated preparation of *N*-Methyl pyridinium salt **4** using similar conditions used by Boesrma (**Scheme II**). The salts prepared by Donohoe were intended for ammonia-free Birch reductions which gave positive results giving *N*-methyl dihydropyridine **5**. The biggest

challenge encountered by Donohoe with *N*-Methyl protecting groups was removal of the protecting group using various deprotection procedures already developed [2-3]. It become apparent that removal of methyl protecting groups was difficult.

For this reason, Donohoe further investigated the use of different protecting groups prepared from either aryl halides or alkyl triflates and pyridinium ester **6**. Initial studies involved benzyl iodide and homoallyl triflate since removal of the protecting groups would be easy by use of palladium-catalyzed hydrogenolysis or palladium-catalyzed deallylation [6,14], respectively. The synthesis of the pyridinium salts again started from the *di*-substituted pyridine **6** (**Scheme III**) [7-8].

Other electron-rich aryl protecting groups such as 4-methoxybenzyl and 3,4-dimethoxybenzyl protecting groups were also investigate by Donohoe during



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preparation of pyridinium salts **9** and **10**, respectively (Scheme IV) [7-9,15-16]. The synthesis of *para*-methoxybenzyl iodide (PMB-I) started from commercially available 4-methoxybenzyl alcohol while the synthesis of 3,4-dimethoxybenzyl bromide (DMB-Br) started from commercially available 3,4-dimethoxybenzaldehyde [10-13].

In this paper we report the relative stability and reactivity of these aryl halides towards the *di*-substituted pyridine **6** in preparation of pyridinium salts. The relative stability that is reported involved leaving the products in top bench and how they react with *di*-substituted pyridine **6**.

EXPERIMENTAL SECTION

Materials

All reactions involving organometallics or other moisture sensitive reagents were carried out under an atmosphere of argon and performed using standard vacuum line techniques and flame dried glassware. Reactions described as being performed at 0 °C were cooled by means of ice bath.

THF, Et₂O and CH₂Cl₂ were dried by passage through a column of aluminum oxide (activated, basic, Brockmann 1, standard grade). H₂O and MeOH were distilled. All other solvents were used as supplied (Analytical or HPLC grade) without further purification.

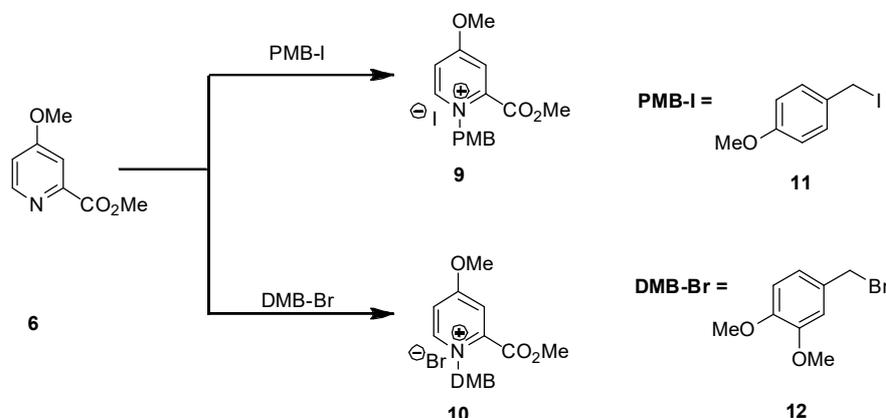
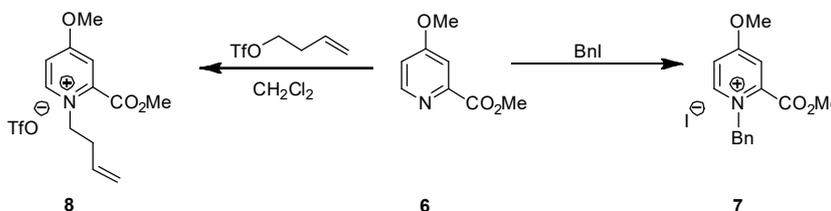
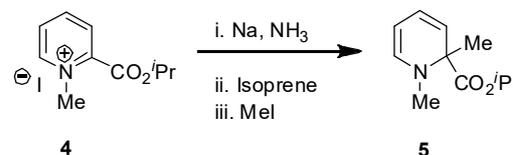
Column chromatography was performed using silica gel (Kieselgel 60). Thin Layer Chromatography (T.L.C) was performed on Merck plates, aluminium sheets coated with silica gel 60 F₂₅₄. Plates were visualized either by UV light (254 nm), iodine, ammonium molybdate (7% in 10% ethanolic sulphuric acid), or 1% aqueous KMnO₄.

All organometallic reagents were used as supplied.

Instrumentation

Infra-red spectra were recorded as thin film (film) or as KBr discs (KBr) using a Bruker Tensor 27 FT-IR. Selected peaks are reported as cm⁻¹.

NMR spectra were recorded on a Bruker DPX 400 (¹H: 400 MHz and ¹³C: 100.6 MHz), Bruker AV-400 (¹H: 400 MHz and ¹³C: 100.6 MHz) spectrometers, in chloroform-d₁ and referenced to residual solvent peaks or to SiMe₄ as an internal standard. Chemical shifts σ , are reported in parts per million (ppm), with the abbreviations s, d, t, q, br and m denoting singlet, doublet, triplet, quartet, broad and multiplet, respectively.



Coupling constants (J) are measured in Hertz and are calculated using a first order approximation. Carbon chemical shifts are quoted in ppm and are referenced using residual solvent signals. Proton and carbon assignments was performed with the aid of COSY (correlated spectroscopy), DEPT and HMQC (heteronuclear multiple quantum correlation) to establish the $H^1 - C^{13}$ coupling.

Low resolution mass spectra (m/z) were recorded on either a VG Masslab 20-250 instrument (ESI), or Platform Micromass instrument (CI, NH_3 or FI). Major peaks are listed with intensities quoted as percentages of the base peak. Accurate mass measurements (HRMS) were recorded on a GCMS machine or a VG Autospec instrument (conducted by Mr. R. Procter). Positive ion spectra were calibrated relative to PEG using tetraoctylammonium bromide as a lock mass.

Procedure

Methyl 4-methoxypicolinate (6)

Picolinic acid (10.00 g, 81.00 mmol) and sodium bromide (1.00 g, 8.10 mmol) were dissolved in thionyl chloride (70 mL) and the mixture was heated under reflux for 16 h. The reaction was concentrated *in vacuo* and cooled to 0 °C. Methanol (35 mL) was added cautiously and the reaction was heated under reflux for 36 h. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (100 mL) followed by addition of Na_2CO_3 (12.80 g, 120 mmol) and the mixture stirred for 3 h. Water (100 mL) was added and the reaction was extracted with CH_2Cl_2 (5 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2 , Et_2O) and re-crystallized (hexane) to furnish the product **6** (9.20 g, 68%) as colorless needles. 1H NMR spectrum (400 MHz; $CDCl_3$): δ 8.50-8.46 (1H, m, ArH), 7.63-7.59 (1H, m, ArH), 6.94-6.90 (1H, m, ArH), 3.94, 3.85 (6H, 2s, 2 × OCH_3); ^{13}C NMR spectrum (100 MHz; $CDCl_3$): δ 166.5 (CO_2CH_3), 165.7, 150.9, 149.5, 113.0, 111.1 (ArC), 55.5, 52.9 (OCH_3). Spectroscopic data matched those reported in the literature [9].

(3,4-dimethoxyphenyl)-methanol (13)

3,4-Dimethoxybenzaldehyde (10.00 g, 60.00 mmol) was dissolved in THF- H_2O (50 mL:2 mL) before the addition of $NaBH_4$ (10.00 g, 60.00 mmol) at 0 °C. The reaction was monitored by TLC and after all the starting material was consumed (after 10 to 15 min), the reaction mixture was quenched with H_2O (50 mL) and extracted with Et_2O (3 × 50 mL), dried (Na_2CO_3), filtered and concentrated *in vacuo* to furnish the product **13** as colorless oil which was directly used in the next step. 1H NMR spectrum (400 MHz; $CDCl_3$): δ 6.92-6.83 (3H, m,

ArH), 4.61 (2H, s, CH_2OH), 3.88, 3.87 (OCH_3), 1.87 (1H, br.s, OH); ^{13}C NMR spectrum (100 MHz; $CDCl_3$): δ 149.1, 148.5, 133.6, 119.4, 111.0, 110.4 (ArC), 65.3 ($ArCH_2OH$), 55.9, 55.8 (OCH_3).

4-(Bromomethyl)-1,2-dimethoxybenzene (12)

A solution of phosphorus tribromide (2.40 mL, 24.00 mmol) in Et_2O (10 mL) was added dropwise to a stirred solution of **13** (10.10 g, 60.00 mmol) in Et_2O (50 mL) at 0 °C and warmed slowly to room temperature. After 1 h at room temperature, the reaction was washed sequentially with brine (40 mL), $NaHCO_3$ (40 mL, saturated aqueous solution) and brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to furnish the product (12.80 g, 92% over two steps) as a white solid. 1H NMR spectrum (400 MHz; $CDCl_3$): δ 6.98-6.92 (2H, m, ArH), 6.82 (1H, d, J 8.2 Hz, ArH), 4.52 (2H, s, CH_2Br), 3.91, 3.89 (6H, 2s, 2 × OCH_3); ^{13}C NMR spectrum (100 MHz; $CDCl_3$): δ 149.2, 149.0, 130.2, 121.5, 111.9 (ArC), 55.9 (2 × OCH_3), 34.5 (CH_2Br).

(3,4,5-trimethoxyphenyl)-methanol (14)

3,4,5-Trimethoxybenzaldehyde (5.00 g, 25.50 mmol) was dissolved in THF- H_2O (20 mL-1 mL) before the addition of $NaBH_4$ (1.00 g, 25.50 mmol). The reaction monitored by TLC and after all the starting material was consumed (after 10 to 15 min), the reaction mixture was quenched with H_2O (50 mL) and extracted with Et_2O (3 × 50 mL), dried (Na_2CO_3), filtered and concentrated *in vacuo* to furnish the product **14** as colorless oil which was directly used in the next step. 1H NMR spectrum (400 MHz; $CDCl_3$): δ 6.57 (2H, s, 2 × ArH), 4.60 (2H, s, CH_2OH), 3.84 (6H, s, OCH_3), 3.82 (3H, s, OCH_3); ^{13}C NMR spectrum (100 MHz; $CDCl_3$): δ 153.3, 137.1, 136.8, 103.0 (ArC), 65.4 ($ArCH_2OH$), 56.0 (OCH_3).

5-(Bromomethyl)-1,2,3-trimethoxybenzene (15)

A solution of phosphorus tribromide (0.86 mL, 9.20 mmol) in Et_2O (10 mL) was added dropwise to a stirred solution of **14** (4.54 g, 23.00 mmol) in Et_2O (50 mL) at 0 °C and warmed slowly to room temperature. After 1 h at room temperature, the reaction was washed sequentially with brine (50 mL), $NaHCO_3$ (50 mL, saturated aqueous solution) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to furnish the product **15** (6.00 g, 98% over two steps) as a white solid. 1H NMR spectrum (400 MHz; $CDCl_3$): δ 6.63 (2H, s, 2 × ArH), 4.47 (2H, s, CH_2Br), 3.88 (6H, s, 2 × OCH_3), 3.85 (3H, s, OCH_3); ^{13}C NMR spectrum (100 MHz; $CDCl_3$): δ 153.3, 133.2, 106.0 (ArC), 60.9, 56.1 (OCH_3), 34.33 (CH_2Br).

4-Methoxybenzyl bromide (16)

A solution of phosphorus tribromide (1.25 mL, 13.15 mmol) in Et₂O (5 mL) was added dropwise to a stirred solution of 4-methoxybenzyl alcohol (5.15 g, 37.30 mmol) in Et₂O (15 mL) at 0 °C and warmed slowly to room temperature. After 1 h at room temperature, the reaction was washed sequentially with brine (30 mL), NaHCO₃ (30 mL, saturated aqueous solution) and brine (30 mL), dried (MgSO₄) and concentrated *in vacuo* to furnish the product **16** (7.40 g, quant.) as an oil. ¹H NMR spectrum (400 MHz; CDCl₃): δ 7.34 (2H, d, *J* 8.8 Hz, ArH), 6.88 (2H, d, *J* 8.6 Hz, ArH), 4.52 (2H, s, CH₂), 3.83 (3H, s, OCH₃); ¹³C NMR spectrum (100 MHz; CDCl₃): δ 159.7, 130.4, 129.9, 114.2 (ArC), 55.3 (OCH₃), 34.0 (CH₂).

4-Methoxybenzyl iodide (11)

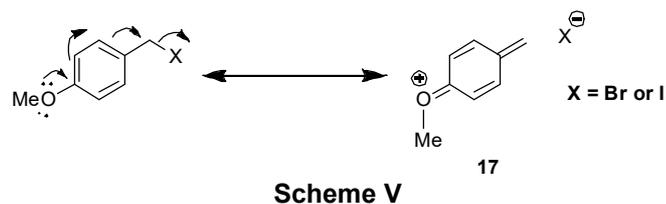
To a stirred solution of 4-methoxybenzyl bromide **16** (3.20 g, 15.92 mmol) in acetone at 0 °C was added sodium iodide (4.77 g, 31.84 mmol) and warmed slowly to room temperature and stirred for 2 h at this temperature while the reaction vessel wrapped in an aluminium paper foil. The resulting mixture was filtered and the acetone was removed *in vacuo*. Petrol (15 mL) was added and the mixture filtered and the solvent removed *in vacuo* to furnish the product without need for further purification. ¹H NMR spectrum (400 MHz; CDCl₃): δ 7.33 (2H, d, *J* 8.6 Hz, ArH), 6.82 (2H, d, *J* 8.6 Hz, ArH), 4.48 (2H, s, CH₂), 3.79 (3H, OCH₃); ¹³C NMR spectrum (100 MHz; CDCl₃): δ 159.2, 131.3, 130.0, 114.3 (ArC), 55.3 (OCH₃), 6.6 (CH₂).

1-(3,4-Dimethoxybenzyl)-4-methoxy-2-(methoxycarbonyl)pyridinium bromide salt (10)

Pyridine ester **6** (0.50 g, 3.00 mmol) was added to a stirred solution of 3,4-dimethoxybenzyl bromide **12** (0.69 g, 3.00 mmol) in Et₂O (5 mL) and stirred for 48 h under an atmosphere of argon at room temperature. The solvent was removed *in vacuo*, and the residue washed with dry THF (2 × 10 mL). The resulting solid was dried under high vacuum to furnish the pyridinium salt (1.19 g, 99%) as a colorless powder. The results match those reported in the literature [9].

RESULT AND DISCUSSION

After learning that aryl halides such as benzyl iodide and 4-methoxybenzyl iodide react with *di*-substituted pyridines to give pyridinium salts our investigations started with formation of pyridinium salt from 4-methoxybenzyl bromide **16** rather than the iodide **11** earlier prepared by Donohoe [5,7]. Preparation of the 4-methoxybenzyl bromide **16** followed the procedure used by Donohoe. Unfortunately, mixing the bromide **16** with the pyridine **6** in different solvents only gave back



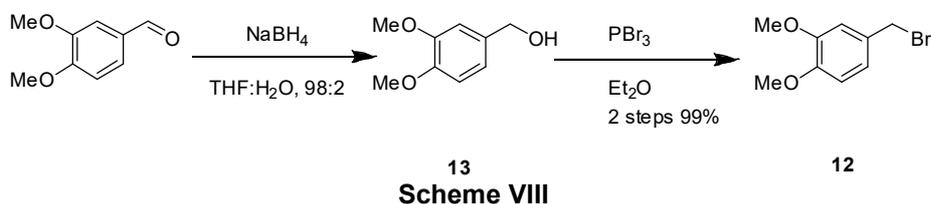
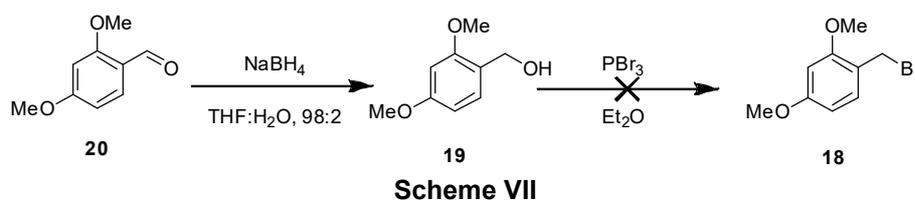
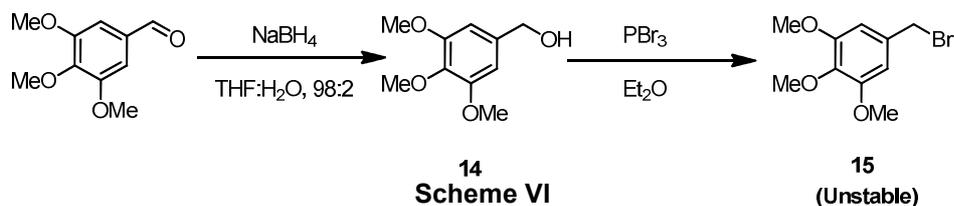
the reactants. Preparation of 4-methoxybenzyl iodide **11** also followed the procedure used by Donohoe. In small scale 4-methoxybenzyl iodide was easily prepared and isolated but it was found that the 4-methoxybenzyl iodide was quite unstable especially when prepared in large scale. It also decomposed during purification process and upon prolonged exposure to light.

These results showed that the iodide decomposed much faster than the bromide. This could be attributed to the fact that iodide is a much better leaving group than bromide ion when expelled from the benzyl ring through delocalisation of the lone pair of electrons from the electron-rich oxygen atom to give structure **17** (**Scheme V**).

The resonance form **17** would be an ideal intermediate to increase reactivity between the pyridine and the aryl halide. For this reason, it was decided that other electron-rich benzyl rings be investigated. 3,4,5-Trimethoxybenzyl bromide **15** was therefore prepared from cheaply commercially available 3,4,5-trimethoxybenzaldehyde *via* the alcohol **14** before converting it to the bromide using procedure followed by Donohoe [7,15-18]. Reduction of the benzaldehyde to the alcohol **14** was successfully achieved by use of NaBH₄ in a solution of THF : H₂O in a ratio of 97:3, respectively.

Unfortunately, preparation of bromide **15** proved difficult since during purification the bromide decompose rapidly giving black slurry (**Scheme VI**). This would be due to the high electron density in the ring which easily kicks out the strategically placed bromide atom. It was therefore noted that benzyl bromide **16** was stable on the bench while 3,4,5-trimethoxybenzyl bromide **15** decomposed much easily.

Further investigation led to preparation of 2,4-dimethoxybenzyl bromide **18** which was thought to have less electron density than a trimethoxybenzyl ring. Careful choice of 2,4-dimethoxybenzyl bromide **18** was done due to its strategically placed methoxy groups at *ortho* and *para* position in the benzene ring to effectively delocalize its electrons. Preparation of **18** started with the commercially available 2,4-dimethoxybenzaldehyde **20** by reduction using NaBH₄ to give to the alcohol **19** in excellent yields (**Scheme VII**). Unfortunately, conversion of the alcohol **19** to the bromide **18** led to decomposition during



purification even though the products could be detected in the crude products by use of NMR and Mass spectrum.

A closer look to the 3,4,5-trimethoxybenzyl bromide **15** and 2,4-dimethoxybenzyl bromide **18** shows that, even though the 3,4,5-trimethoxybenzyl bromide has three methoxy groups, two of the methoxy groups are not strategically placed to delocalize their electrons as effectively as the 2,4-dimethoxybenzyl bromide **18** whose two methoxy groups are strategically placed hence increasing the electron density of the ring towards the bromide atom. Therefore for this reason, the stability of the two compounds **15** and **18** on the bench are relatively similar.

Having established the instability of 4-methoxybenzyl iodide **11**, 2,4-dimethoxybenzyl bromide **18** and 3,4,5-trimethoxybenzyl bromide **15**, it was decided that 3,4-dimethoxybenzyl bromide **12** be investigated since it had one strategically placed methoxy group at position 4 of the benzene ring and one at position 3 that would sufficiently increase the electron density to the ring without much delocalization. Following similar procedures employed earlier, compound **12** was prepared from commercially available 3,4-dimethoxybenzaldehyde via the alcohol **13**, which was treated with phosphorous tribromide to yield the product **12** as white crystals in quantitative yields over the two steps (Scheme VIII) and the spectroscopic data of the product matched that reported in the literature.

Although benzyl halides **11**, **18** and **15** decomposed rapidly, **12** was stable in air for up to two weeks before it would start decomposing slowly to a

black colored slurry. For this reason, **12** required to be stored in cool temperature. Preparation of the 3,4-dimethoxybenzyl iodide using various methods only yield decomposed products. This was again attributed to the fact that iodide is a better leaving group than bromide ion.

This phenomenon of decomposition of benzyl bromide derivatives would match their degree of reactivity and the electron density in the aromatic ring due to the electron donation by the methoxy groups. 3,4,5-Trimethoxybenzyl bromide having the most methoxy groups has the highest electron donation hence electron density. It is therefore the least stable bromide when left on the bench. 2,4-Dimethoxybenzyl bromide is the second least stable bromide due to its strategically placed two methoxy groups at ortho and para positions to the leaving group (bromide ion). 3,4-Dimethoxybenzyl bromide has lower electron density in the ring than 2,4-dimethoxybenzyl bromide since one of the methoxy groups is at the meta position to the leaving group hence not strategically placed to delocalize its electrons into the ring and displace the bromide ion. Therefore 3,4-dimethoxybenzyl bromide is more stable than 3,4,5-trimethoxybenzyl bromide and 2,4-dimethoxybenzyl bromide when left on the bench.

Lastly 4-methoxybenzyl bromide is the most stable and least reactive towards *di*-substituted pyridine **6**. The order of the relative stability and reactivity of the benzyl bromides toward *di*-substituted pyridine **6** is in the following order (Fig. 1).

Besides benzyl iodide which is stable in air, only 4-methoxybenzyl iodide was prepared and characterized

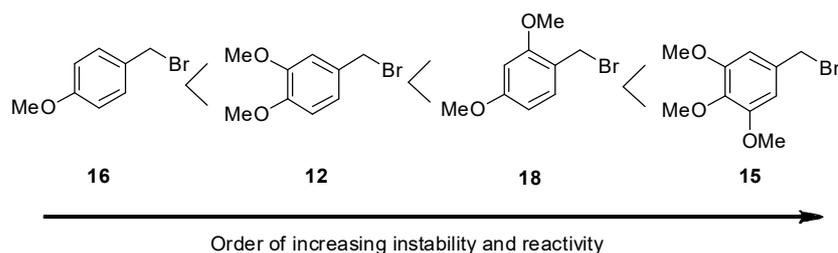


Fig 1.

but decomposed slowly when left in air and was sensitive to light during the work-ups. 3,4-dimethoxybenzyl iodide, 2,4-dimethoxybenzyl iodide, and 3,4,5-trimethoxybenzyl iodide were not isolated since they decomposed rapidly.

Reaction of benzyl bromide and 4-methoxybenzyl bromide **16** with di-substituted pyridine **6** only returned the reactants while reaction of 3,4-dimethoxybenzyl bromide **12** with di-substituted pyridine **6** gave the salt in quantitative yields. Reaction of the 2,4-dimethoxybenzyl bromide **18** and 3,4,5-trimethoxybenzyl bromide **15** with the di-substituted pyridine **6** were not investigated due to their instability.

CONCLUSION

From this experiment, it has been shown that the higher the electron density of benzyl bromide derivative, the higher its reactivity towards nucleophilic attack and low is its stability in normal laboratory conditions. Reactions of 2,4-dimethoxybenzyl bromide and 3,4,5-trimethoxybenzyl bromide were not investigated since they were quite unstable. This is also true with the benzyl iodide derivatives which were unstable except for the benzyl iodide and 4-methoxybenzyl iodide which are slightly stable but decomposed when exposed to light. These reactions may further be investigated in terms of kinetics and mechanisms. This could give further insights of the proposed mechanism for expulsion of the leaving group.

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