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Change of Orientation in Electrophilic Substitution of Benzaldehydes by *O*-Alkyloximation Derivatives

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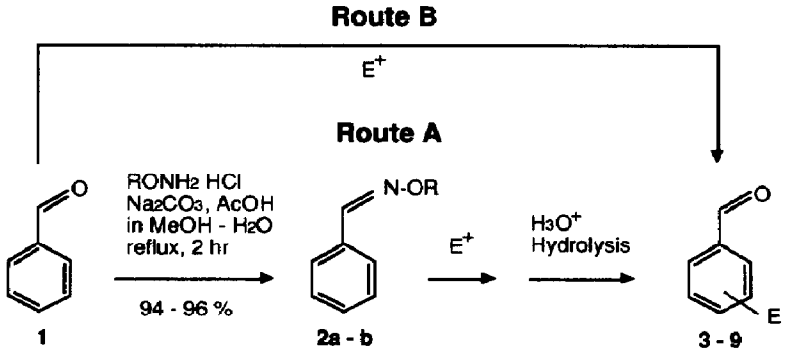
Abstract: By the introduction of *O*-alkyloxyimino group, orientation in electrophilic substitution of benzaldehyde can be selectively controlled.

Substituted benzaldehydes (**4**, **5**, **7** and **9**) are important intermediates in the production of medicines, agricultural chemicals, and functional polymers. Several methods for their preparation of substituted benzaldehydes have been reported.[1-5] For example, it is known that direct halogenation of benzaldehyde (**1**) provides 3-halobenzaldehyde (**6**, **8**).[5,6] The substitution at the 3-position in this halogenation is due to the presence of strongly electron- attracting formyl group and it is difficult to obtain 2- and/or 4-halobenzaldehyde directly from **1**. At present, the following three methods are known to obtain substituted benzaldehyde at the 2- and/or 4-positions: (1) oxidation of 4-halotoluene,[7,8] (2) hydrolysis of 4-halobenzal chloride,[9] and (3) oxidation of 4-halobenzyl alcohol[10,11]. However, all these methods are not free from serious contamination because of strong oxydation conditions used. To the best of our knowledge, there is no method available to produce 2- and/or 4-halobenzaldehyde directly from **1**.

In this communication, we report a new and simple method to obtain 2- and/or 4-halobenzaldehyde derivatives from 1 by means of *O*-alkyloximation[12] of the formyl group. This *O*-alkyloxyimation can also be applied to nitration in order to selectively obtain 3-nitrobenzaldehyde.

Benzaldehyde was converted to *O-alkyloxime derivatives*[13] (**2a** and **2b**) in excellent yields (94 - 96 %) by the reaction using *O*-alkylhydroxylamine (Fig. 1). The resulting *O*-alkyloxime derivatives



	R
2a	Me
2b	Et

	E
3	2-NO_2
4	3-NO_2
5	2-Cl
6	3-Cl
7	4-Cl
8	3-Br
9	4-Br

Fig. 1 Reaction scheme (route A and route B)

Table 1 Synthesis of **3** - **9** from **1**, **2a** and **2b**

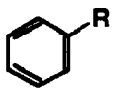
Starting material	Route	Reaction	Reagent	Reaction condition (Solvent)	Ratio (%) Position 2-	3-	4-	Total yield (%)
2a	A				0	100	0	92
2b	A	Nitration	HNO_3	5°C x 1 h (H_2SO_4)	0	100	0	94
1	B				20	80	0	96
2a	A				36	0	64	75
2b	A	Chlorination[a]	Cl_2	50°C x 1 h (CCl_4)	32	0	62	76
1	B				0	100	0	82
2a	A				3	0	97	72
2b	A	Bromination[a]	Br_2	50°C x 1 h (CCl_4)	2	0	98	74
1	B				0	100	0	75

a) $AlCl_3$ was used as a catalyst.

were readily halogenated or nitrated under the conditions shown in Table 1.[14,15] The halogenation of **2a** and **2b** produced a mixture of products substituted at the 2- or 4-position (route A), while the direct hydrogenation of benzaldehyde gave a product substituted only at the 3-position (route B). This indicates that substitution orientation in the halogenation of benzaldehyde was changed by *O*-alkyloxymation of the aldehyde group. On the contrary, the nitration of *O*-alkyloxime **2a** and **2b** gave a product substituted only at the 3-position (route A), while the direct nitration[3,4] of benzaldehyde (**1**) yielded a mixture (2 : 8) of products substituted at the 2- or 3-position (**3** and **4**, route B).

The mechanism of substitution of O-alkyloxyiminobenzaldehyde can be explained by the change of frontier electron density of benzene ring and energy level of HOMO (Highest Occupied Molecular Orbital).[16] As shown in Table 2 and Fig. 2, an electron-attracting formyl group (-10.05 eV) is convertible to an electron-donating group (-9.37 eV) by alkyloxymation. This electron donating ability of *O*-alkyloxyimino group is very similar to that of methyl group (-9.44 eV). Its electron-donating property results in increase of frontier electron density of the benzene ring, especially around the carbon atoms at the 2- and 4-positions (Fig. 2). This change of frontier electron density due to introduction of *O*-alkyloxyimino group can explain the different substitution orientation be-

Table 2 Energy level of HOMO in substituted benzene derivatifves



	-OMe	-CH=NOMe	-Me	-H	-CHO	-CN	-CH=$\overset{+}{N}$HOMe
(eV)	-9.11	-9.37	-9.44	-9.75	-10.00	-10.10	-13.85

tween **1** and **2a** in Fig. 1.

On the other hand, the change of orientation was not observed in the nitration reaction. This related to the fact that HNO_3 and H_2SO_4 are used in the nitration (Table 1). *O*-Alkyloxyimino group is protonated in the acidic condition and its electron-attracting ability (-13.85 eV) becomes stronger than that of the original formyl group. Probably, this extremely low energy level allows to yield a product substituted only at the 3-position in the nitration of *O-alkyloxyiminobenzaldehyde* as shown in Fig. 2, although a product subtituted at the 2-position is produced as a by-product in the nitration of benzaldehyde.

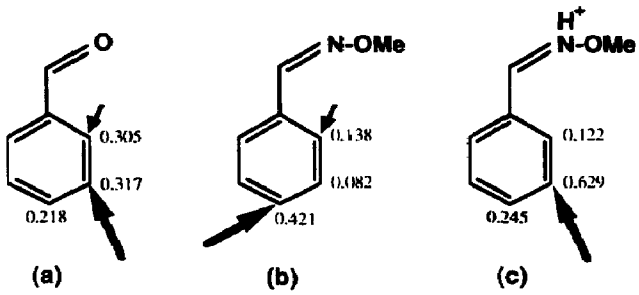


Fig. 2 Frontier electron density of HOMO.

As shown in Fig. 1, *O*-alkyloxyimino group can readily be hydrolyzed using an acid catalyst, and, therefore, the parent aldehyde can easily be reproduced (**4**, **5**, **7** and **9**). We conclude that O-alkyloxymation is useful for selective electrophilic substitution reactions. This is because the energy level of HOMO can be drastically changed by the introduction of *O*-alkyloxyimino group.

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13) Benzaldehyde *O*-alkyloximes (**2a** and **2b**) from **1**: 1 (21.4 g, 0.2 mol), *O*-alkylhydroxylamine hydrochloride (0.2 mol) and Na_2CO_3 (11.7 g, 0.11 mol) were dissolved in MeOH (20 mL) and water (60 mL). AcOH (2 mL) was then added to the mixture with stirring to adjust the pH to 4.5, and the mixture was heated at reflux for 2 h. After cooling, water and $CHCl_3$ were added to the solution. The organic layer was separated, washed with water, then dried ($MgSO_4$). The solvent was evaporated and the residue was distilled *in vacuo* to give the products.

14) 2-, 4-Halobenzaldehyde (**5** ,**7** and **9**) from **2a** and **2b**: A solution of **2a** or **2b** (0.1 mol), CCl_4 (70 mL) and $AlCl_3$ (1.0 g) were treated with Cl_2 or Br_2 (0.1 mol) over a period of 1 h at 50 °C. After

cooling, water was added to the solution. The organic layer was separated, washed with water, then dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the crude products obtained (2- and/or 4-halobenzaldehyde *O*-aklyloximes) were hydrolyzed with 25% HCl (100 mL) at 70 °C for 3 h. The products were isolated by distillation or filtration.

15) 3-Nitrobenzaldehyde (**4**) from **2a** and **2b**: To a solution of **2a** or **2b** (0.1 mol) and 98% H_2SO_4 (70 g, 0.7 mol) was added 94% HNO_3 (6.6 g, 0.1 mol) over a period of 1 h at 5 °C. The mixture was then stirred for 2 h at 5 °C and poured into water (250 mL). The solution was heated at 70 °C for 3 h. After cooling, the precipitate was filtered and washed with water.

16) Caliculation of frontier electron density and energy level of HOMO in benzaldehyde derivatives (Table 2 and Fig. 2) were carried out with a MATERIA of Teijin System Technology (Japan).

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