One Pot Conversion of Carboxylic Acids to Aldehydes through Treatment of Acyloxy-9-borabicyclo[3.3.1]nonanes with Lithium Aluminum Hydride in the Presence of Pyridine

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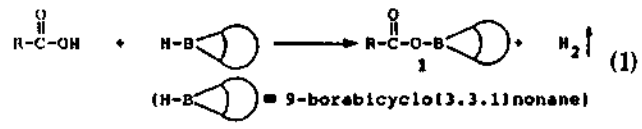
The development of simple routes to aldehydes from readily available carboxylic acids is an important goal in organic chemistry. Some useful reagents[1] including thexylhaloboranes[2] have appeared to be promising for such direct transformation.

In addition to them, the new methodology utilizing the commercially available 9-borabicyclo[3.3.1]nonane (9-BBN) provides another convenient route to obtain aldehydes[3]. The acyloxy moiety of acyloxy-9-BBNs (**1**), readily formed from the reaction of carboxylic acids and 9-BBN with evolution of 1 equiv of hydrogen (eq. 1), was readily reduced by lithium 9-boratabicyclo[3.3.1]nonane (Li 9-BBNH) and the reduction stops at the aldehyde stage.



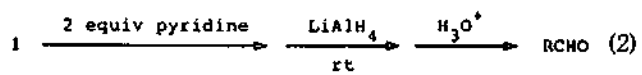
(1)

The acyloxy group of **1** was also readily converted to the aldehyde stage through stepwise treatment with *tert*-butyllithium and 9-BBN. This interesting reaction suggests that **1** possess adequate structural and electronic features for the conversion of acyloxy group to the aldehyde stage readily.

In the course of exploring a practical method for such direct conversion, we found that lithium aluminum hydride (LAH) in the presence of excess pyridine effects the desired transformation in good yields.

LAH possesses 4 equiv of hydride, and all are strong enough to reduce both aliphatic and aromatic acyloxy groups to their final alcohol stages. Actually, when 1 was treated with 1 equiv LAH at room temperature, the acyloxy group was completely reduced to the alcohol stage (Table 1). However, in the presence of 2 equiv of pyridine the reduction stops at the aldehyde stage.[4]

This system reduces aromatic carboxylic acids examined, except nitrobenzoic acids, in 80-95% yields (eq. 2), as shown in Table 1. The unsubstituted acids, such as benzoic and naphthoic acids, are readily reduced to the corresponding



(2)

aldehydes in yields of 78-88%. Derivatives containing substituents such as alkyl, alkoxy, and halogeno groups on benzene ring are readily accommodated. However, the yields for nitrobenzoic acids are significantly low to about 60%, due to the reduction of nitro group itself by this system. Dicarboxylic acids, such as phthalic and terephthalic acids, are also reduced to the dialdehydes in more than 90% yields.

On the other hand, the yields in the reduction of aliphatic series examined are much lower than those in the aromatic series, showing approximately 50% yields.

Table 1. Yields of Aldehydes in the Reduction of Representative Carboxylic Acids through Treatment of Acyloxy-9-BBN (1) with Lithium Aluminum Hydride in the Presence of Pyridine in Tetrahydrofuran at Room Temperature[a]

Acid	Yield of aldehyde(%)[b]	Acid	Yield of aldehyde(%)[b]
benzoic	78 (0)[c](63)[d]	*m*-nitrobenzoic	59
o-toluic	93	*p*-nitrobenzoic	61
m-toluic	92	1-naphthoic	85
p-toluic	95 (86)[d]	2-naphthoic	88
o-anisic	88	phthalic	90
m-anisic	88	terephthalic	94 (84)[d]
p-anisic	89	caproic	57 (0)[c]
o-chlorobenzoic	83	stearic	52
m-chlorobenzoic	79	isobutyric	50
p-chlorobenzoic	84	diphenylacetic	55
o-nitrobenzoic	61		

[a] 2 Equiv of pyridine was added to 1 and reacted with 1 equiv of LAH for 0.5 h at room temperature. [b] Yields based on (2,4-dinitrophenyl)hydrazones. [c] No pyridine added. [d] Yields based on the analytically pure aldehydes isolated by the sodium bisulfite procedure[2a,b].

The following procedure for the reduction of *p*-toluic acid is illustrative. To the mixture of *p*-toluyloxy-9-BBN (53 mmol) in THF (10 m*l*), prepared from the reaction of equivalent *p*-toluic acid and 9-BBN[3], 8.56g (106 mmol) of pyridine and 35.3 m*l* of 1.5 M LAH solution in THF (53 mmol) were injected in sequence. The mixture was then stirred for 0.5 h at room temperature. Analysis of an aliquot with (2,4-dinitrophenyl)hydrazine indicated *ca.* 95% conversion.

The rest of the reaction mixture (50 mmol) was hydrolyzed with 4 N HCl for 6 h at room temperature. The separated organic layer was then subjected to the sodium bisulfite isolation procedure[2a,b]. Thus 5.17 g (86%) of analytically pure *p*-tolualdehyde isolated after evaporation of volatiles, following treatment of the adduct with formaldehyde, was obtained.

References

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3. (a) J. S. Cha, J. E. Kim, S. Y. Oh and J. D. Kim, *Tetrahedron Lett.*, 28, 4575 (1987); (b) J. S. Cha, S. Y. Oh, K. W. Lee, M. S. Yoon, J. C. Lee and J. E. Kim, *Bull. Korean Chem. Soc.*, **9**, 48 (1988). (c) J. S. Cha, J. E. Kim, M. S. Yoon and Y. S. Kim, *Tetrahedron Lett.*, 28, 6231 (1987).
4. Although the role of pyridine in this reduction is not clear, we believe that pyridine behaves as a coordinator to the boron atom of **1** resulted in a borane-pyridine complex which inhibits the hydride attact from LAH to the carbonyl carbon.

Evidence of Radical Ion Pair for Singlet Oxygen Reaction of Bilirubin and Related Oxopyrromethenes. Oxidation Potential of Bilirubin and Related Oxopyrromethenes

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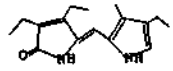
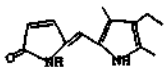
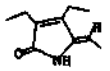
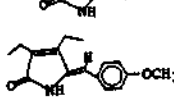
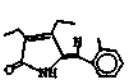
The phototherapy for treating neonatal jaundice is used since the caused bilirubin IX-α (BR) in the human body is destroyed by light illumination[1-3]. BR is destroyed by photoreaction under aerobic or anaerobic conditions. Photooxygention of BR in the presence of a sensitizer, rose bengal, gave methylvinyl maleimide, hematinic acid and two propendyopents[4-5]. The oxomonopyrromethenes (**6**, **7**, **8**, see table 1) resisted dye-sensitized photooxygenation; whereas oxodipyrromethenes (**1**, **2**, see Table 1) and mesobilirubin (MBR) reacted with singlet oxygen ($^1O_2$) to give products from cleavage of exocyclic enamide double bonds[6]. Kinetic study showed that highly substituted oxodipyrromethenes are more reactive toward $^1O_2$[6]. Thus radical ion mechanism[6] was suggested for singlet oxygen reaction of BR and BR-related compounds.

In this work singlet oxygen reaction rate ($^1O_2$ generated by the thermal method) and oxidation potential of BR and BR-related enamines (mainly oxopyrromethenes) were measured as evidences for radical ion pair mechanism in the singlet oxygen reaction of the enamine derivatives (BR and BR-related substrates).

Khan and Kasha[7] reported that $^1O_2$ is generated by reaction of NaOCl with H_2O_2. BR and BR-related substrates (1 mg) was dissolved in 5 m*l* of methanol. The solution (1 m*l*) was taken in 3 m*l* UV cuvette and 1 m*l* of 30%-H_2O_2 and 0.2 m*l* of NaOCl solution (effective chlorine 10%) were added. The percent change of the absorbance of BR and BR-related substrates were measured within 3 min reaction time. They are summarized in Table 1. MBR, BR and oxodipyrromethenes (**1**,**2**) are reactive; whereas BV and oxomonopyromethenes (**6**,**7**,**8**) are unreactive toward $^1O_2$ generated chemically. For comparison, K_R values, reaction rate constant of enamine substrates from ref. 6 was also given in the table. The same reactivity tendency of BR and BR-related substrates is shown for $^1O_2$ generated photochemically or thermally.

Cyclic voltammograms of BR and BR-related substrates were measured within 0~+1.2 volt *vs.* Saturated Calomel Electrode (SCE) with polarographic analyzer and universal

Table 1. Reaction Rate Constants and Percent Absorbance Changes of Bilirubin and Its Model Compounds with $^1O_2$ Generated by Photochemical and Thermal Methods, Respectively. Oxidation Potential of Bilirubin and Its Model Compounds

Bilirubin and its model compounds	% change of absorbance in 3 min[b]	K_R ($\times 10^9$ $M^{-1}S^{-1}$)[c]	Oxidation potential *vs.* S.C.E.(volt)
 1	37.2%	1.4 1.0[a]	0.24
 2	43.9%	0.1	0.32
Mesobilirubin IX-a (MBR) 3	60.8%	0.79[a]	0.24, 0.37 0.60
Bilirubin IX-a (BR) 4	33.1%[d]	0.28[a]	0.32, 0.44 0.64
Biliverdin IX-a (BV) 5	0%	0.0024	0.34, 0.60
 6	0%	0	0.80
 7	0%	0	0.98, 1.06
 8	0%	0	1.07, 1.12

[a] With 0.2% vol. conc. NH_4OH. [b] In methanol. [c] Taken from ref. 6. in methanol.