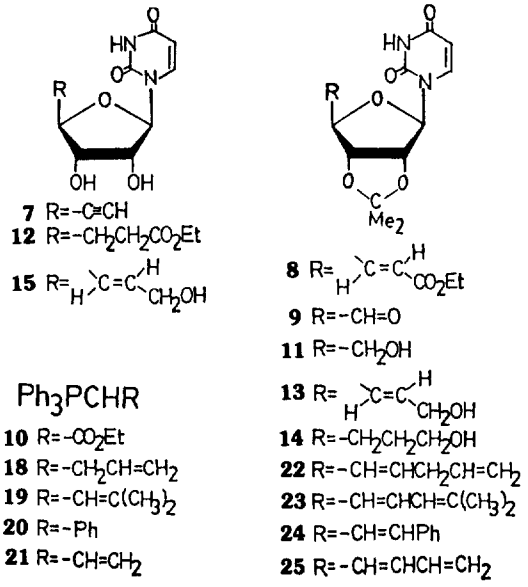

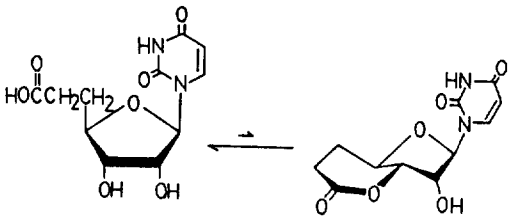

16 **17**

ted. We also prepared a carboxylic acid derivative, **16** by hydrolysis of **12** with potassium hydroxide in ethanol. However, lactonizations of compound **12** and **16** were not successful at all. Difficulty in lactonization of **12** and **16** should be attributable to the instability of **17** owing to the strain of the trans-fused bicyclic system.

It was not necessary to isolate aldehyde **9** from the reaction mixture in DMSO in its reaction with the stabilized ylide such as **10**. However, in the reaction with nonstabilized ylides, aldehyde **9** must be purified to some extent and thus the oxidation of **11** with DMSO-DCC is not appropriate because of difficulty in isolation of **9**. Pure **9** could be obtained in 85% yield by oxidation of **11** with chromium trioxide-pyridine complex in methylene chloride-dimethylformamide at room temperature and by precipitating **9** in benzene-hexane. The Wittig reactions of isolated **9** with ylides **18-21** in THF afforded chain-extended nucleosides **22-25** in high yields, respectively. The stereochemistry of newly generated double bonds varied with reaction condition and the ratios of the cis and trans isomers of **22-25** were not rigorously determined.

The results of the present work indicate that Wittig reactions employing both stabilized and nonstabilized ylides are generally applicable to synthesis of chain-extended nucleosides and that bicyclic lactone nucleoside **17** is unstable and rather exists in the carboxylic acid form, **16**. And interesting biological activities of the nucleosides synthesized in the present work are expected.

Acknowledgement. This work was supported by a grant from the Korea Science and Engineering Foundation.

References

1. V. Nelson, H. S. El Khadem, B. K. Whitten, and D. Sesselman, *J. Med. Chem.*, **26,** 1071 (1983).
2. (a) H. Follman, *Angew. Chem. Int. Ed. Engl.*, **13,** 77 (1974).
3. D. C. Baker and R. P. Crews, *J. Med. Chem.*, **26,** 1530 (1983).
4. M. Iwakawa, O. R. Martin, and W. A. Szarek, *Carbohydr. Res.*, **121,** 99 (1983).
5. (a) L. M. Lerner, *Carbohydr. Res.*, **44,** 13 (1975), (b) L. M. Lerner, *J. Org. Chem.*, **43,** 2469 (1978).
6. R. A. Sharma and M. Bobek, *J. Org. Chem.*, **43,** 367 (1978).
7. P. Howgate, A. S. Jones, and J. R. Titensor, *Carbohydr. Res.*, **12,** 403 (1970).

An Improved Synthesis of Aldehydes from Carboxylic Acid Esters with Diisobutylaluminum Hydride in the Presence of *o*-Anisidine

Seong Heon Kim, Jeong Hyo Kim, and Nung Min Yoon*

Department of Chemistry, Sogang University, Seoul 121-742. *Received October 12, 1988*

The synthesis of aldehydes from carboxylic acid derivatives is one of the most important reactions in organic synthesis, and many useful reducing agents have been developed.[1] Recently thexylchloroborane-dimethyl sulfide[1a] and thexylbromoborane-dimethyl sulfide[1b] are reported to be excellent reagents for the partial reduction of carboxylic acids and their salts to the corresponding aldehydes. However only a few reagents are knwon for the transformation of carboxylic acid esters to the corresponding aldehydes. Representative metal hydrides for such purposes are diisobutylaluminum hydride[2] (DIBAH), lithium tri-*tert*-butylaluminum hydride[3] (LTBA), and bis(4-methylpiperazinyl) aluminum hydride[4,5] (BMPA). Of these reagents, LTBA reduces phenyl esters of aliphatic acids to aldehydes in yields of approximately 70%, however, can not be applied for aromatic acids. Although BMPA is effective for both aliphatic and aromatic esters, and gives 50-80% yields of aldehydes, the reaction requires the longer reaction

Table 1. Partial Reduction of Carboxylic Acid Esters to Aldehydes with DIBAH in the Presence of *o*-Anisidine in Toluene at −78°C

entry		*o*-anisidine[a]	DIBAH[a]	yield[b] of aldehyde %
1	ethyl butyrate	0.5	1.5	87
		0.5	1.7	84
		2.0	3.0	94[c] (88[d])
2	ethyl caproate	2.0	3.0	95[c] (83[c])
				81[e]
3	ethyl isovalerate	2.0	3.0	86[c]
4	ethyl isobutyrate	2.0	3.0	89[c] (77)
5	ethyl cyclohexane-carboxylate	2.0	3.0	89
		1.0	2.2	84
6	ethyl pivalate	2.0	3.0	69 (55)
		1.0	2.2	56
7	ethyl 4-chlorobutyrate	2.0	3.0	94
		1.0	2.0	82
8	ethyl 3-chloropropionate	2.0	3.0	83
9	ethyl 2-bromopropionate	2.0	3.0	73 (62)
10	ethyl crotonate	2.0	3.0	26
		1.0	2.0	23
11	ethyl benzoate	2.0	3.0	78[c] (62[d])
12	isopropyl benzoate	2.0	3.0	83[c] (74[c])
13	ethyl 4-methylbenzoate	2.0	3.0	47[c] (16[c])
14	ethyl 4-methoxybenzoate	2.0	3.0	18[c] (8[c])
15	ethyl 4-chlorobenzoate	2.0	3.0	75 (53)
16	ethyl 4-nitrobenzoate	2.0	3.0	76 (48[c])
17	ethyl cinnamate	2.0	3.0	26[c]

[a] Mmol per mmole of ester [b] Yields were estimated by 2,4-DNP. Yields obtained by DIBAH alone are shown in parenthesis. [c] Yields were estimated by GLC. [d] Yields reported by Zakharkin Ref. 2a [e] Isolated yield.

time (6-10 h), usually at elevated temperature (65 °C). On the other hand, DIBAH has been generally utilized for the aldehyde synthesis from esters. However the yields of aromatic aldehydes (48-70%) are considerably lower than those of aliphatic aldehydes (80-88%)[2a]. Recently we have found the yields of aldehydes are improved substantially by adding *o*-anisidine to esters before the DIBAH addition. Therefore we have tested the generality of this method with representative aliphatic and aromatic esters and the results are reported in this communication.

The reduction is typically carried out as described for ethyl benzoate below. A mixture of ethyl benzoate (1 mmol) and *o*-anisidine (2 mmol) in toluene was charged into the flask which was cooled to − 78 °C by a dry ice-acetone bath. To this was added 2 m*l* of DIBAH (3 mmol) in toluene for 20-25 min with release of 40 m*l* of hydrogen gas. The reaction mixture was kept at − 78 °C for additional 10 min, then hydrolyzed with 8 m*l* of 4N HCl and was stirred for 1 h at room temperature. Saturating the aqueous layer with NaCl, the organic layer was separated and dried over anhydrous sodum sulfate. The GLC analysis showed a 78% yield of benzaldehyde, using 10% Carbowax 20 M with naphthalene as an internal standard.

The results are summarizd in Table 1. As shown in the Table, the less hindered linear carboxylic acid esters and the more hindered ethyl isobutyrate and ethyl cyclohexanecarboxylate give all the good yields of aldehyde (86-95%) considerably higher than those obtained by DIBAH alone(entry 1-5). Actually we isolated caproaldehyde in 81% yield, following the sodium bisulfite adduct procedure described in Ref. 1a. However a bulkier derivative such as ethyl pivalate gives a lower yield (69%), presumably due to the steric hindrance(entry 6). Halogen-substituted derivatives also show good results; however, the position of halogen substituent on carbon chain seems to effect the aldehyde yields. Thus, when halogen substituent is at γ-carbon (i.e., ethyl 4-chlorobutyrate) the yield is excellent, however when the halogen is substituted more closely (i.e., ethyl 3-chloropropionate and ethyl 2-bromopropionate), the yields of the corresponding aldehydes are 83 and 73% respectively(entry 7, 8, 9). In aromatic series, ethyl benzoate, isopropyl benzoate, ethyl 4-chlorobenzoate, and ethyl 4-nitrobenzoate all give good yields of aldehydes, about 18-28% higher than those obtained by DIBAH alone (entry 11, 12, 15, 16). However, the two benzoates which have electron releasing substituent, such as ethyl 4-methylbenzoate and ethyl 4-methoxybenzoate, give poor yields of aldehydes(entry 13, 14). The two, α,β-unsaturated esters tested, ethyl crotonate and ethyl cinnamate both give very poor yields(entry 10, 17).

In conclusion, the aldehyde synthesis from esters by DIBAH is improved substantially by the addition of *o*-anisidine, especially for aromatic esters. However, α,β-unsaturated esters and benzoic acid esters which have an electron donating substituent give poor results.

Acknowledgement. The financial support of this work by the Korea Science and Engineering Foundation is gratefully acknowledged.

References

1. (a) H. C. Brown, J. S. Cha, N. M. Yoon, and B. Nazer, *J. Am. Chem. Soc.*, **106,** 8001 (1984); *J. Org. Chem.*, **52,** 5400 (1987). (b) J. S. Cha, J. E. Kim, and K. W. Lee, *J. Org. Chem.*, **52,** 5030 (1987), and references therein.
2. (a) L. I. Zakharkin and I. M. Khorlina, *Tetrahedron Lett.*, 619 (1962). (b) G. Bruno, *Brochure,* Ethyl Corporation, Baton Rouge, LA., U.S.A. 1968, and 1972. (c) E. Winterfieldt, Synthesis, 617 (1975).
3. P. M. Weissman and H. C. Brown, *J. Org. Chem.*, **31,** 283 (1966).
4. M. Muraki and T. Mukaiyama, *Chem. Lett.*, 215 (1975).
5. T. D. Hubert, D. P. Eyman, and D. F. Wiemer, *J. Org. Chem.*, **49,** 2279 (1984).