A New Method for the Preparation of Active Esters Using Di-2-pyridyl Carbonate

Sunggak Kim* and Young Kwan Ko

Department of Chemistry, Korea Advanced Institute of Science and Technology, Seoul 131, Korea

The use of di-2-pyridyl carbonate in the presence of a catalytic amount of 4-dimethylaminopyridine is found to be very effective in the preparation of various active esters.

Active esters have been widely used as versatile synthetic intermediates, especially in peptide synthesis, and the development of a variety of active esters has been studied extensively.[1,2] During our continuing studies on the synthetic utility of di-2-pyridyl carbonate (2-DPC),[3] we have found that it can be effectively used as a coupling reagent for the preparation of various active esters such as 2-pyridyl, succinimido, phthalimido, benzotriazol-1-yl, and *p*-nitrophenyl.

For the preparation of 2-pyridyl esters using 2-DPC [reaction (1)], reaction of benzoic acid with 1 equiv. of 2-DPC in the presence of 0.1 equiv. of 4-dimethylaminopyridine (DMAP)[4] in dichloromethane at room temperature for 1 h afforded 2-pyridyl benzoate in 85% yield, while the reaction using triethylamine or pyridine as a base did not proceed to an observable extent at room temperature in 6 h. Further reactions were carried out with equimolar amounts of carboxylic acids and 2-DPC in the presence of 0.1 equiv. of DMAP in dichloromethane at room temperature, and were normally complete within 1 h. The water-soluble 2-hydroxypyridine by-product can be completely removed by the usual work-up or can be recovered in high yields (80—90%) by precipitation with diethyl ether or light petroleum. Using this procedure, several carboxylic acids including *N*-protected α-amino acids were cleanly converted into the corresponding 2-pyridyl esters. Typical isolated yields were: MeCO–O–2-Py, 90%; Boc-Leu-O-2-Py, 81%; Boc-Ala-O-2-Py, 72%.

$$RCO_2H + \underset{\text{2-DPC}}{\text{Py–O–C(:O)–O–Py}} \rightarrow RCO_2Py + PyOH \quad (1)$$

$$RCO_2H + R'OH + \text{2-DPC} \rightarrow RCO_2R' + PyOH \quad (2)$$

Conditions: CH_2Cl_2, 0.1 equiv. of DMAP R′OH = HOSu, HOPt, HOBt, or HONp.

Py = 2-pyridyl

2-DPC can be successfully utilized as a coupling reagent for the preparation of several active esters using *N*-hydroxy succinimide (HOSu), *N*-hydroxyphthalimide (HOPt), 1-hydroxybenzotriazole (HOBt), and *p*-nitrophenol (HONp) as the alcoholic component [reaction (2)]. With equimolar amounts of the carboxylic acid, 2-DPC, and the alcoholic component in the presence of 0.1 equiv. of DMAP in dichloromethane at room temperature, the reaction was normally complete within 1 h to give satisfactory yields of the corresponding active esters: typical isolated yields: MeCO-OSu, 86%; PhCO-OSu, 92%; Z-Leu-OSu, 85%; Z-Phe-OSu, 87%; Boc-Ala-OSu, 76%; PhCO-OPt, 88%; Z-Leu-OPt, 88%; PhCO-OBt, 90%; MeCO-OBt, 85%; Z-Phe-OBt, 88%; PhCO-ONp, 89%; Z-Leu-ONp, 85%; Boc-Ala-ONp, 78%.

The identities of the active esters were confirmed by comparison of n.m.r. and i.r. spectral data, $[\alpha]_D$ values, and m.p.s with reported data; active esters of *N*-protected α-amino acids were obtained without observable racemization.

We gratefully acknowledge financial support from Korea Science and Engineering Foundation.

Received, 14th January 1985; Com. 063

References

1 E. Gross and J. Meienhofer, 'The Peptides, Analysis, Synthesis, Biology,' vol. 1, Academic Press, New York, 1979, and references cited therein.
2 For recently developed reagents, see: H. Ogura, T. Kobayashi, K. Shimizu, K. Kawabe, and K. Takeda, *Tetrahedron Lett.*, 1979, 4745; K. Kurita and H. Imajo, *J. Org. Chem.*, 1982, **47**, 4584; M. Ueda, H. Oikawa, and T. Teshrogi, *Synthesis*, 1983, 908.
3 S. Kim, J. I. Lee, and Y. K. Ko, *Tetrahedron Lett.*, 1984, 4943.
4 For excellent reviews, see: G. Höfle, W. Steglich, and H. Vorbrüggen, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 569; E. F. V. Scriven, *Chem. Soc. Rev.*, 1983, **12**, 129.