Tetrahedron Letters,Vol.23,No.11,pp 1201-1204,1982 0040-4039/82/111201-04$03.00/0
Printed in Great Britain

A NEW METHOD OF ACYLATION AT β-POSITION OF ALIPHATIC AMINES[1]

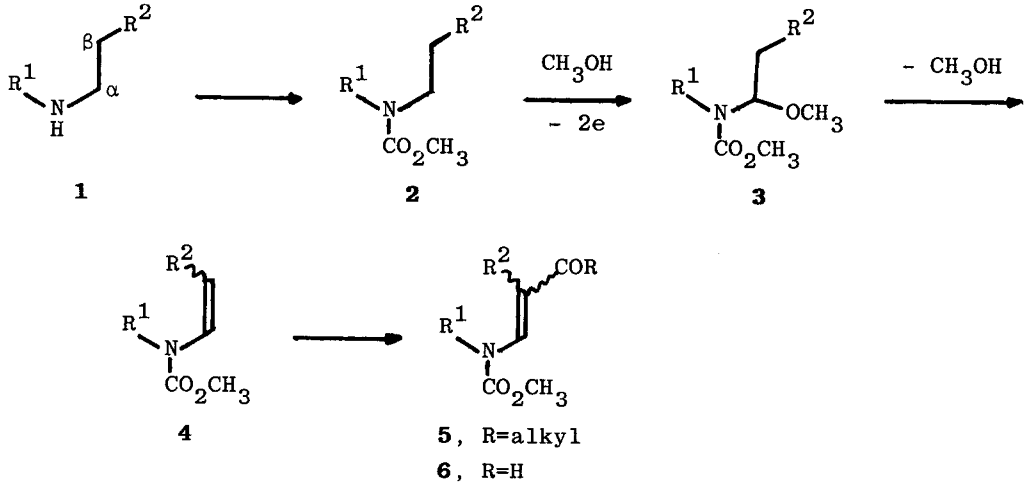
Tatsuya Shono,* Yoshihiro Matsumura, Kenji Tsubata, and Yoshihiro Sugihara
Department of Synthetic Chemistry, Faculty of Engineering,
Kyoto University, Yoshida, Sakyo, Kyoto 606, Japan

A new method to introduce an acyl or a formyl group to β-position of aliphatic amines was studied using encarbamates, prepared from α-methoxycarbamates, as key intermidiates.

We have already reported[2] the C-C bond forming reaction at α-position of aliphatic amines (**1**) utilizing α-methoxycarbamates (**3**) as the starting compounds which can be prepared by anodic oxidation of carbamates (**2**). We wish to report herein a convenient method of C-C bond formation at β-position of **1** as shown in Scheme I, in which encarbamates (**4**), prepared from **3**, are acylated at the β-position by the Friedel-Crafts or the Vilsmeyer reaction.

Preparation of **4** was easily achieved by heating **3** (100-120 °C) with catalytic amount of ammonium chloride.[5] Yields and boiling points of **4** are indicated in Notes.[6] The electrophilic reactions with **4** were carried out as follows.

Scheme I



1 **2** **3** **4**

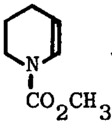
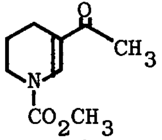
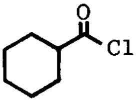
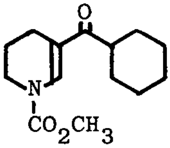
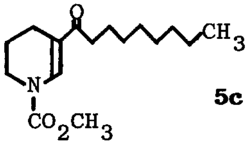
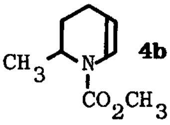
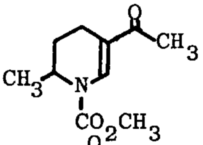
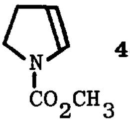
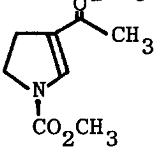
5, R=alkyl

6, R=H

(1) Acylation. Acylation of **4** was carried out under the conditions of the Friedel-Crafts reaction.[7] To a stirred solution of acid chloride (50 mmol) in CH_2Cl_2 (15 ml) was added dropwise stannic chloride (50 mmol) over a period of 5 min at - 70 °C under an atmosphere of nitrogen and the reaction mixture

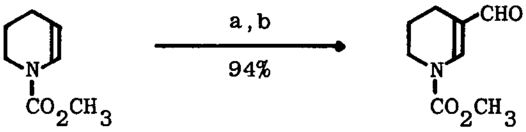
was stirred for 15 min. To the mixture was added dropwise a solution of **4** (5 mmol) in CH_2Cl_2 (5 ml) in a period of 30 min. After the reaction was completed, usual working-up and isolation by column chromatography (silica gel) gave **5**.

Table I. Reaction of **4** with Acid Chlorides.

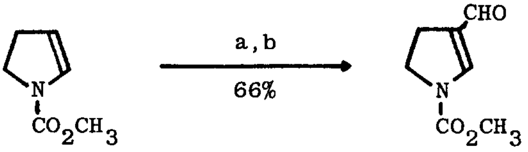
4	Acid Chloride	Reaction Temp. (°C)	Reaction Time (h)	**5**^{a}	(% Yield)
 **4a**	CH_3COCl	- 70 → r.t.	20	 **5a**	58
4a		- 60 → r.t.	14.5	 **5b**	85
4a		- 70 → r.t.	9	 **5c**	69
 **4b**	CH_3COCl	- 70 → r.t.	5	 **5d**	70
 **4c**	CH_3COCl	- 70	3	 **5e**	32

a. References and Notes 8.

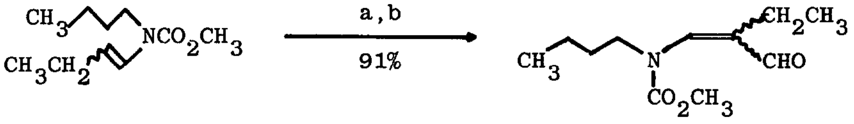
(2) Formylation. The Vilsmeyer reaction[9] with **4** gave β-formylencarbamates **6**. General procedure is as follows. Phosphorus oxychloride (8.5 mmol) was added dropwise to DMF (8.5 mmol) at 10-20 °C in a period of 3 min and the mixture was stirred for 20 min. To the cooled mixture (5 °C) was added ethylene dichloride (10 ml) and then a solution of **4** (7.08 mmol) in ethylene dichloride (5 ml) over a period of 30 min. The solution was stirred at 0-5 °C for 1 h and refluxed for 15 min. Working-up with aqueous sodium acetate was followed by isolation through column chromatography (silica gel) to afford **6a-c**.[10,11] Results are shown in the following equations (eqs. 1-3).



4a **6a** (1)



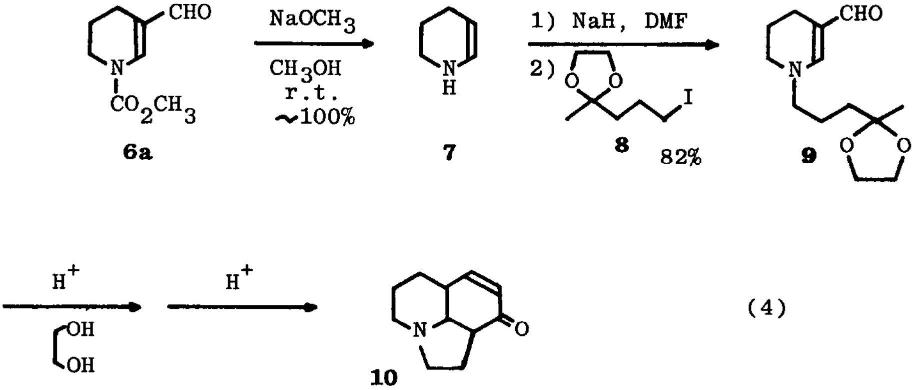
4c **6b** (2)



4d[11] **6c** (3)

a : DMF, $POCl_3$, CH_2ClCH_2Cl, 0-5 °C. b : AcONa, H_2O, Δ.

As an example of the application of the Vilsmeyer reaction with encarbamates, a hydrolulolidine derivative (**10**) was synthesized from **6a** (eq. 4). Thus, to a solution of **6a** (10 mmol) in methanol (10 ml) was added a catalytic amount of sodium methoxide, and the reaction mixture was stirred at room temperature for 4 h. After the solvent was evaporated, the residue was purified by column chromatography on alumina to yield **7** (~100% yield). Alkylation of **7** with 5-iodo-2-pentanone ethylene ketal (**8**) was achieved by the successive addition of sodium hydride (6.8 mmol) and **8** (6.8 mmol) into the solution of **7** (4.5 mmol) in dry DMF (15 ml). The reaction mixture was stirred at 0 °C for 2.5 h and at room temperature overnight to afford **9** (82% yield). Although **9** has already been synthesized from nicotinaldehyde, the yield is low.[12] The cyclization of **9** to **10** can be easily carried out by acetalization of **9** and subsequent treatment with acid as described in the literature.[12]



6a **7** **8** **9** **10** (4)

As shown above, β-acyl- and β-formylencarbamates were obtained easily from **1**, and these products are useful intermediates for the synthesis of important nitrogen containing compounds such as alkaloids. Further investigation on the reaction of encarbamates and utilization of β-acyl- and β-formylencarbamates in synthesis will be reported shortly.

Acknowledgment. We thank the Yamada Science Foundation for supporting a part of this work.

References and Notes

1. Electroorganic Chemistry. 56.
2. (a) T. Shono, Y. Matsumura, and K. Tsubata, *J. Am. Chem. Soc.*, **103**, 1172 (1981). (b) T. Shono, Y. Matsumura, and K. Tsubata, *Tetrahedron Lett.*, **22**, 2411 (1981). (c) T. Shono, Y. Matsumura, K. Tsubata, and J. Takata, *Chem. Lett.*, **1981**, 1121.
3. Carbon-Carbon bond formation at the β-position of nitrogen is also achievable successfully by the reaction of enamines[4] with some electrophiles. The starting compounds in this case, however, are not amines but aldehydes or ketones.
4. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovics, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).
5. (a) T. Shono, Y. Matsumura, and H. Hamaguchi, *J. Am. Chem. Soc.*, **97**, 4264 (1975). (b) K. Nyberg, *Synthesis*, **1976**, 545.
6. **4a**: 96% yield, bp 102 °C (23 mm). **4b**: 68% yield, bp 52 °C (0.35 mm). **4c**: 91% yield, bp 88 °C (22 mm). **4d**: 94% yield, bp 115-118 °C (23 mm).
7. G. A. Olah, "Friedel-Crafts Chemistry", Wiley, New York (1973).
8. The melting points and nmr spectra (olefinic proton) of the products **5a-e** are as follows: **5a**, mp 52.8-53.3 °C from ether, nmr (CCl_4) δ 7.90; **5b**, oil, nmr (CCl_4) δ 7.87; **5c**, oil, nmr (CCl_4) δ 7.91; **5d**, oil, nmr (CCl_4) δ 7.83; **5e**, mp 107.5-109 °C from hexane-AcOEt (2:1), nmr (CCl_4) δ 7.47.
9. R. M. Silverstein, E. E. Ryskiewicz, and C. Willard, "Organic Syntheses", Collective Vol. 4, Wiley, New York (1963), p. 831.
10. The melting points and nmr spectra (olefinic proton) of the products **6a-c** are as follows: **6a**, mp 182-183 °C from ether, nmr (CCl_4) δ 7.63; **6b**, mp 102-103 °C from hexane-AcOEt (3:8), nmr (CCl_4) δ 7.42; **6c**, oil, nmr (CCl_4) δ 7.42.
11. Stereochemistry of **4d** and **6c** was not determined.
12. E. Wenkert, K. G. Dave, and R. V. Stevens, *J. Am. Chem. Soc.*, **90**, 6177 (1968).

(Received in Japan 8 December 1981)