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Introduction of an Acetonyl Grouping at the C(3) Position of 2,3-Dehydropiperidine via Rearrangement of (β-Aminocyclopropyl)carbonyl Intermediate

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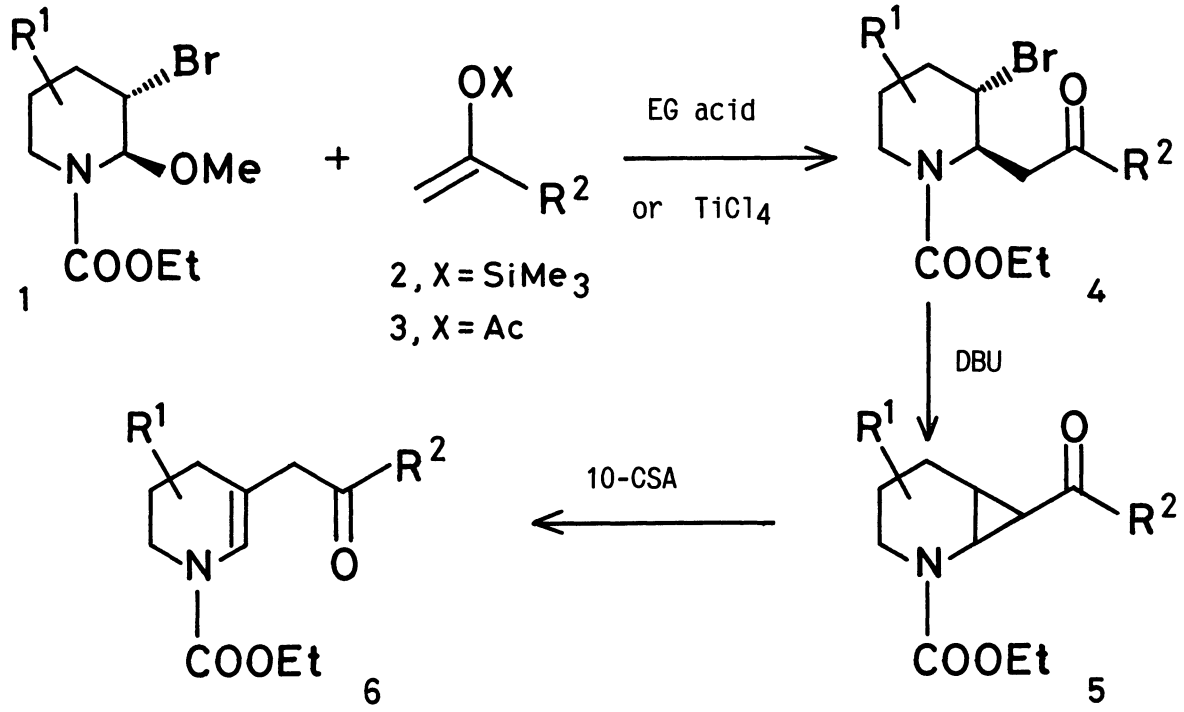
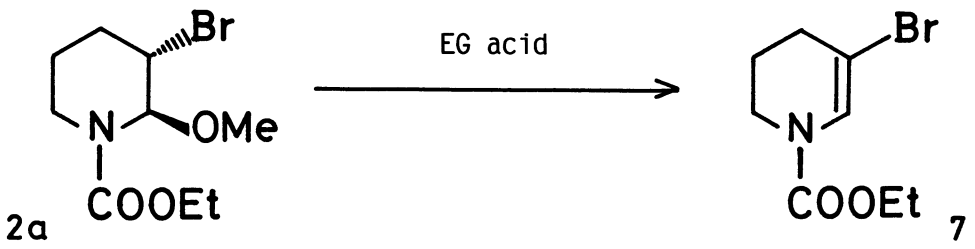
A new and efficient method for introducing 2-oxoalkyl group at the C(3) position of 2,3-dehydropiperidine has been explored based on rearrangement tactics of (β-aminocyclopropyl)carbonyl intermediate.

The acid-, base-, or thermal-promoted ring opening of (β-alkoxycyclopropyl)-carbonyl derivatives has been shown to be a versatile method for obtaining functionalized 1,4-dicarbonyl compounds.[1] However, little attention has been paid to the preparation and rearrangement of their β-aminocyclopropane derivatives.[2] In continuation of our research to extend the electrochemical functionalization of nitrogen containing heterocycles,[3a,4] we became interested in the regioselective alkylation of the β-position of encarbamate based on the above rearrangement tactics. In this paper, we report a facile preparative access to N-ethoxycarbonyl-3-acetonyl-2,3-dehydropiperidine derivatives **6** from β-bromo-



N,O-acetals **1** via cyclopropanation at the C(2), C(3) positions followed by selective cleavage of the resulting three membered ring of **5**.[5)]

As shown in the Scheme, the aldol reaction of N-ethoxycarbonyl-β-bromo-N,O-acetals **1**, obtained by electrochemical halomethoxylation of 2,3-dehydropiperidines,[3a)] with enol silyl ethers **2** or an enol acetate **3** was effected either by using an electrogenerated acid (EG acid)[6)] or Lewis acid[7)] as a catalyst. Thus, the electrolysis of **1a** and the enol silyl ether **2a** in methylene chloride containing lithium perchlorate ($LiClO_4$) and n-Bu_4NClO_4 as an electrolyte and as a source of EG acid at room temperature produced the corresponding adduct **4a** in 92% yield (entry 1).[8)] Treatment of **1a** with EG acid in the absence of an enol silyl ether **2**, however, caused the demethoxylation to give 3-bromo-2,3-dehydropiperidine **7** in 83% yield. On the other hand, the aldol reaction of **1a** with isopropenyl acetate **3** was carried out by using 1.2-1.5 equivalent of titanium tetrachloride ($TiCl_4$) as a catalyst in CH_2Cl_2 to give the adduct **4c** in 85% yield. Reaction of **1a** with ketene silyl acetal **2c** was carried out successfully by using $TiCl_4$ to give the adduct **4d** in 68% yield. Results of the aldol reactions are listed in Table 1.



2a 7

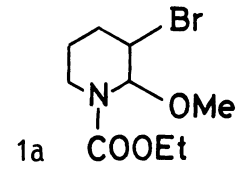
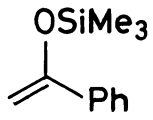
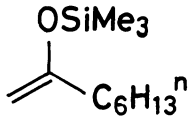
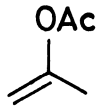
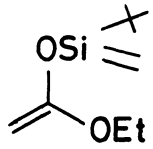
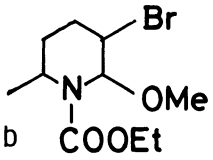
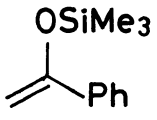
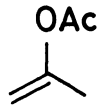
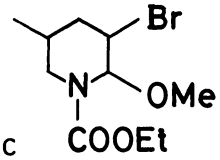
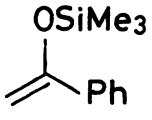
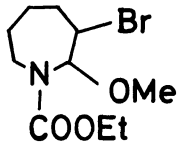
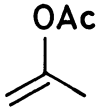
The 1,3-dehydrobromination of **4** to the cyclopropyl ketone **5** was achieved by using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base. Thus, treatment of **4c** with DBU (ca. 1.5 equivalent) at room temperature in toluene and the following usual workup afforded the corresponding cyclopropyl ketone **5c**. IR spectra of **5c** shows absorptions at 1720 and 1700 cm^{-1} due to the ethoxycarbonyl and cyclopropylcarbonyl groups.[9)]

The compound **5c** thus obtained underwent smooth rearrangement on treatment with a small amount of 10-camphorsulfonic acid (10-CSA) in CH_2Cl_2 to give the desired 2-acetonyl-2,3-dehydropiperidine **6c** in 97% yield. The rearrangement of the cyclopropane intermediate **5d** to **6d** with 10-CSA was performed by heating under reflux in toluene (entry 4). Results of the transformation of **4** to **6** are listed in Table 1.

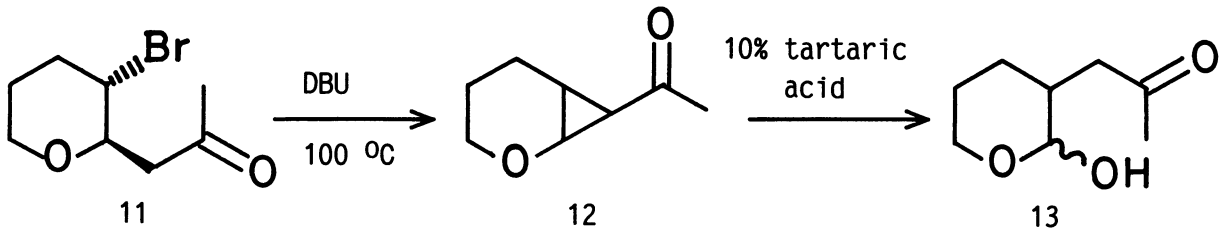
The procedure described here is also applicable to the preparation of N-ethoxycarbonyl-3-acetonyl-1-azacyclohept-2-ene (**10**) from the seven membered N,O-acetal **8** (entry 8). We also attempted to extend this procedure to the pyran derivative. However, acid treatment of **12**, provided by dehydrobromination of **11**, with aqueous 10% tartaric acid produced the lactol **13** in poor yield (20% from **11**).

The present alkylation procedure is versatile due to the easy availability of the starting acetals **1** from simple piperidines,[3a)] since little is known about the regioselective introduction of alkyl substituents at the β-position of encarbamate.

Table 1. Results of the Conversions of 1 to 4 and 4 to 6

Entry	N,O-Acetal 1	Enol olefin 2 or 3	Acid catalyst	Product (Yield/%)[c] from 1	Product (Yield/%)[c] from 4
1	 1a	 2a	EG acid[a]	4a (92)	6a (77)
2	1a	 2b	EG acid[a]	4b (52)	6b (81)
3	1a	 3	$TiCl_4$[b]	4c (85)	6c (97)
4	1a	 2c	$TiCl_4$[b]	4d (68)	6d (69)[d]
5	 1b	 2a	EG acid[a]	4e (52)	6e (80)
6	1b	 3	$TiCl_4$[b]	4f (67)	6f (93)
7	 1c	 2a	EG acid[a]	4g (79)	6g (49)
8	 8	 3	$TiCl_4$[b]	9 (78)	10 (80)[e]

a) Electrolyses were carried out by using 0.5-1.0 mmol of the substrate and 1.2-2.0 equivalent of the nucleophile by passing 0.1-0.2 F/mol of electricity at room temperature in an undivided cell. b) The reactions were carried out by using 1.2-1.5 equivalent of $TiCl_4$ at -78 to 0 °C. c) Based on isolated products. d) The reaction was carried out under reflux in toluene. e) 10-CSA was added at 0 °C in dichloromethane.



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4) S. Torii, T. Inokuchi, S. Takagishi, F. Akahoshi, and K. Uneyama, Chem. Lett., 1987, 639.

5) Almost same investigation with our present work has been presented by T. Shono, Y. Matsumura, M. Oogaki, and O. Onomura at 54th Annual Meeting of the Chemical Society of Japan in Tokyo, April 1987, No. 3IIIG-42; Abstract paper II, p. 995.

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8) Typical procdure for EG-acid catalyzed alkylation of β-bromo-N,O-acetal **1** is as follows: Into an electrolysis vessel were added $LiClO_4$ (5.3 mg, 0.05 mmol) and n-Bu_4NClO_4 (17 mg, 0.05 mmol) and these materials were dried at 100 °C under vaccum for 1 h. To this mixture was added a solution of acetal **1a** (133 mg, 0.5 mmol) and enol silyl ether **2a** (192 mg, 1.0 mmol) in CH_2Cl_2 (3 ml). The entire mixture was electrolyzed under a constant current of 6.7 mA/cm^2 (applied voltage: 10-15 V) at room temperature. The progress of the reaction was monitored by TLC and the reaction was quenched with Et_3N (3 drops) when the starting **1a** was completely consumed. The volatiles were removed on a rotary evaporator and the residue was purified by column chromatography (SiO_2, hexane-AcOEt 5:1) to give 163 mg (92%) of the adduct **4a**.

9) ^1H NMR (60 MHz, $CDCl_3$) δ = 1.22 (t, J = 6.5 Hz, 3, CH_3), 1.30-2.20 (m, 6, CH_2, CH_2), 2.22 (s, 3, $COCH_3$), 2.64 (m, 1, CH), 3.25 (m, 1, CH_2N), 3.68, 3.90 (m, 1, CH_2N), 4.12 (q, J = 6.5 Hz, 2, CH_2O).

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