Pergamon

Tetrahedron Letters, Vol. 37, No. 32, pp. 5715-5718, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01208-7

Regio- and Stereo-selective Introduction of a Bis(methoxycarbonyl)methyl Group into the γ-Position of the Piperidine Skeleton

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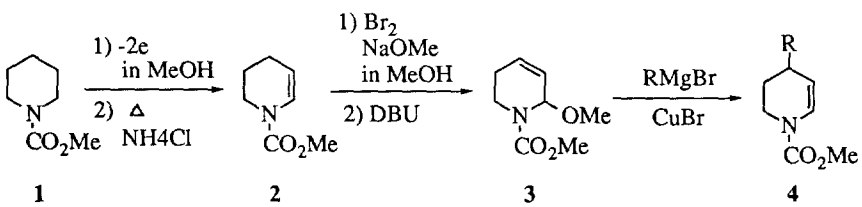
***Abstract*::** A new method for a regioselective introduction of a bis(methoxycarbonyl)-methyl group into the 4-position of the piperidine skeleton was explored, and this method was applied to the preparation of *cis*- and *trans*-2,4-disubstituted piperidines starting from 2-piperidinecarboxylic acid. The key steps in the method involved electrochemical oxidation of carbamates. Copyright © 1996 Elsevier Science Ltd

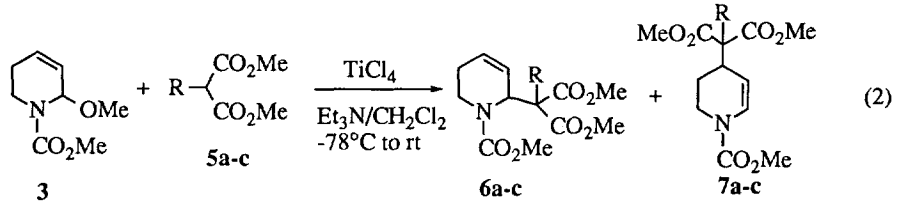
Piperidines possessing substituents at the 4-position are useful synthetic intermediates for a variety of alkaloids.[1] The introduction of a substituent into the 4-position of a piperidine skeleton is conventionally the simplest and most promising method for the preparation of this type of compound, though there have been so far reported very few effective methods.[2] We recently succeeded in the regioselective introduction of alkyl groups to the 4-position of 1-methoxycarbonyl-2-methoxy-1,2,5,6-tetrahydropyridine **3** which could be easily prepared from 1-methoxycarbonylpiperidine **1** by utilizing electrochemical oxidation (eq 1).[3] Our method, however, has not been applicable to a bis(methoxycarbonyl)methyl group (-$CH(CO_2Me)_2$) as one of the introducing alkyl groups in spite of the importance of piperidines, which possess the group or its derived group such as -CH_2CO_2R or -$CHR'CO_2R$ at the 4-position, in the synthesis of some alkaloids.[4] Furthermore, hitherto no methods for the stereoselective introduction of substituents into the 4-position of a piperidine skeleton have been known. We report herein a new method to introduce a bis(methoxycarbonyl)methyl group to the 4-position of a piperidine skeleton with high regio- and stereo-selectivities.



(1)

The key starting compound **3** was prepared according to the route shown in eq 1 (**2**: 83% from **1**, **3**: 58% from **2**).[3] Subsequent addition of $TiCl_4$ to a solution of **3**, dimethyl malonate **5a**, and triethylamine in

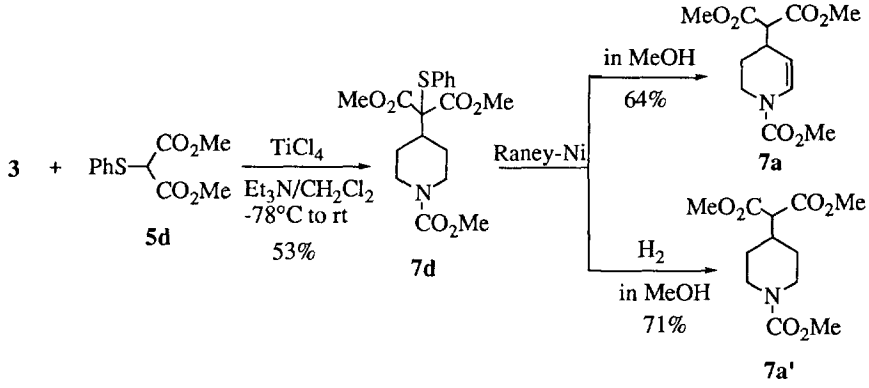
methylene chloride gave only 2-substituted product **6a**, while the reaction of **3** with dimethyl alkylmalonates **5b,c** regioselectively gave the desired 4-substituted products **7b,c** (eq 2). These excellent regioselectivities were explainable in terms of steric repulsion between 1-methoxycarbonyl and the introduced substituent. Namely, bulky nucleophiles such as **5b,c** lead to the formation of 4-substituted piperidines, and a less bulky nucleophile such as **5a** leads to the formation of a 2-substituted product.



(2)

6a	68%	**7a**	0%	**a**: R = H
6b	0%	**7b**	52%	**b**: R = Me
6c	0%	**7c**	91%	**c**: R = Ph

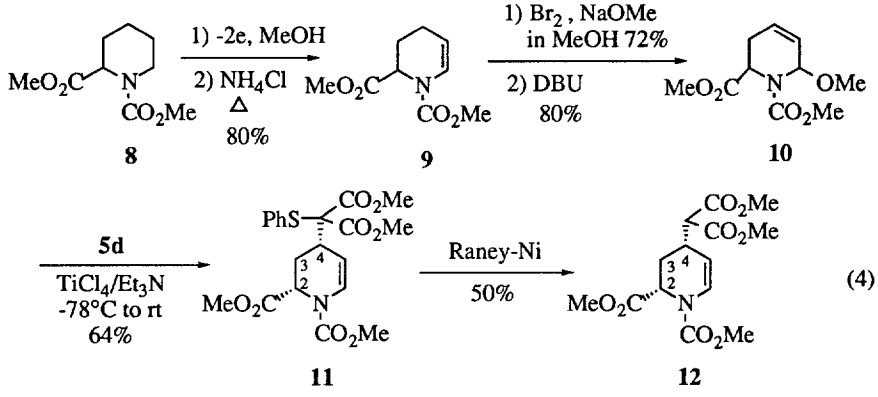
Accordingly, some device was necessary in order to obtain 4-substituted piperidines such as **7a** since the removal of the R group from **7b,c** was difficult. The device we adopted was the use of dimethyl α-phenylthiomalonate **5d** as a nucleophile. In fact, the reaction of **3** with **5d** selectively afforded **7d**, which was easily transformed to **7a** and **7a'**, respectively, by Raney-Ni reduction under different reaction conditions as shown in eq 3.



(3)

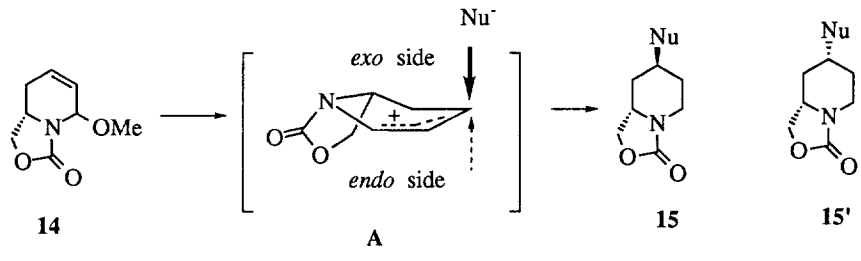
The stereoselective introduction of a bis(methoxycarbonyl)methyl group to the 4-position of a piperidine skeleton was the other objective of our study. For this purpose, we used 2-piperidinecarboxylic acid derivative **8** as a starting compound since the 2-methoxycarbonyl group was removable or convertible to other functional groups [5] after the introduction of a substituent to the 4-position, and the proposed method might be applicable to optically active 2-piperidinecarboxylic acid which was commercially available. Thus, **8** was easily transformed to 6-methoxy-2-piperidinecarboxylic acid ester **10** through 5,6-dehydro-2-piperidinecarboxylic acid ester **9** by a similar procedure to that used in the transformation of **1** to **3**. The reaction of **10** with **5d** regio- and stereo-selectively afforded 4-substituted 2-piperidinecarboxylic acid derivative **11**, which was

converted to **12** by the reduction with Raney-Ni in methanol (eq 4). The structures of **11** and **12** were assigned as *cis*-2,4-disubstituted isomers on the basis of the NMR and NOE spectra.[6]



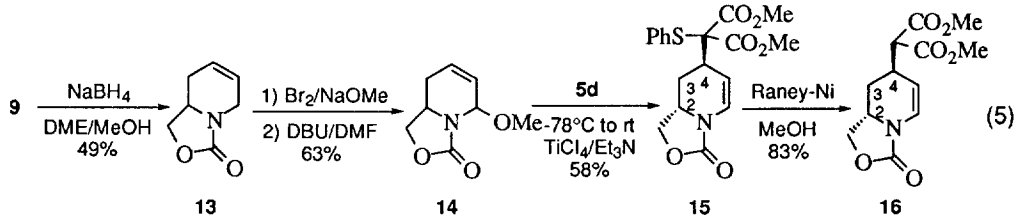
(4)

Next, we attempted to synthesize *trans*-2,4-disubstituted isomers starting from the same starting compound. For this purpose, we prepared a bicyclic compound **14** from **9** in anticipation that treatment of **14** with Lewis acid could generate a cationic intermediate **A**, in which the *endo* side might be more crowded than the *exo* side, to afford a *trans*-2,4-disubstituted isomer **15** (Scheme 1).



Scheme 1 $Nu^- = {}^-C(SPh)(CO_2Me)_2$

The synthesis of **14** from **9** was achieved by the procedure shown in eq 5. When **14** was treated with **5d**, only the *trans*-2,4-disubstituted isomer **15** was generated without any formation of the *cis*-2,4-disubstituted isomer **15'** as we expected. The reduction of **15** with Raney-Ni in methanol gave the *trans*-2,4-disubstituted isomer **16** (eq 5). The stereochemical relationship between 2- and 4-substituents of **15** and **16** was ascertained by the NMR and NOE spectra.[7]



(5)

The application of our method to the synthesis of optically active 4-substituted piperidines starting from optically active 2-piperidinecarboxylic acid is now under investigation.

Acknowledgments: One of the authors (Y.M.) thanks the Japanese Ministry of Education, Science and Culture for a Grant-in-Aid for Scientific Research on Priority Areas (No.7455364), and T.M. thanks the Japan Society for the Promotion of Science (JSPS) for a JSPS Research Fellowship.

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4. For examples, Barco, A.; Benetti, S.; Risi, C.D.; Pollini, G.P.; Romagnoli, R.; Spalluto, G; Zanirato, V. *Tetrahedron*, **1994**, *50*, 2583-2590.
5. For example, Patai, S. ed. "The chemistry of carboxylic acids and esters" Interscience-Publishers, London, **1969**.
6. Compound **11**: mp 130-131°C (from MeOH) ;two conformational isomers were observed in ^{1}H NMR spectrum (0.4/0.6 ratio);^{1}H NMR ($CDCl_3$, 500MHz) δ 1.88-1.95 (m, 1H), 2.69-2.76 (m, 1H), 2.78-2.82 (m, 1H), 3.67 (s, 3H), 3.701 (s, 0.4 x 3H), 3.705 (s, 0.6 x 3H), 3.712 (s, 3H), 3.75 (s, 0.4 x 3H), 3.80 (s, 0.6 x 3H), 4.83 (dd, *J*=2.7, 4.6Hz, 0.4H), 4.96 (dd, *J*=2.7, 4.8Hz, 0.6H), 5.03 (d, *J*=8.7Hz, 0.6H), 5.11 (d, *J*=8.7Hz, 0.4H), 6.83 (ddd, *J*=0.9, 2.7, 8.7Hz, 0.6H), 6.96 (ddd, *J*=0.9, 2.7, 8.7Hz, 0.4H), 7.30-7.48 (m, 5H). A NOESY experiment of **11** confirmed the *cis* configuration; NOE between C-2 proton (δ 4.83 and 4.86) and C-4 proton (δ 2.69-2.76).
   Compound **12**: oil ;two conformational isomers were observed in ^{1}H NMR spectrum (0.4/0.6 ratio);^{1}H NMR ($CDCl_3$, 500MHz) δ 1.76-1.85 (m, 1H) 2.43-2.49 (m, 1H), 2.80-2.85 (m, 1H), 3.30 (d, *J*=8.0Hz, 1H), 3.75 (s, 9H), 3.77 (s, 0.6 x 3H), 3.80 (s, 0.4 x 3H), 4.72 (d, *J*=8.5Hz, 0.6H), 4.79 (d, *J*=8.5Hz, 0.4H), 4.81 (dd, *J*=3.0, 5.1Hz, 0.6H), 4.93 (dd, *J*=3.0, 4.6Hz 0.4H), 6.83 (dd, *J*=1.6, 8.7Hz, 0.6H), 6.96 (dd, *J*=1.6, 8.5Hz, 0.4H).
7. Compound **15**: mp 135-138°C (from MeOH) ;^{1}H NMR ($CDCl_3$, 500MHz) δ 1.71 (ddd, *J*=7.8, 12.4, 14.2Hz, 1H), 2.86 (dd, *J*=3.4, 14.0Hz, 1H), 2.99-3.02 (m, 1H), 3.70 (s, 3H), 3.71 (s, 3H), 3.72-3.78 (m, 1H), 3.90 (t, *J*=8.6Hz, 2H), 4.61 (t, *J*=8.2Hz, 1H), 5.32 (ddd, *J*=1.1, 4.6, 8.3Hz, 1H), 6.75 (dd, *J*=2.3, 8.3Hz, 1H), 7.35 (t, *J*=7.6Hz, 2H), 7.42-7.47 (m, 3H). The structure of **15** was estimated by the observation of NOEs between 2β proton (δ 3.72-3.78) and 3β proton (δ 2.86), and between 3α proton (δ 1.71) and 4α proton (δ 2.99-3.02).
   Compound **16**: oil;^{1}H NMR ($CDCl_3$, 500MHz) δ 1.74 (ddd, *J*=5.9, 11.9, 13.9Hz, 1H), 2.02 (ddd, *J*=1.1, 2.5, 13.7Hz, 1H), 3.10-3.15 (m, 1H), 3.33 (d, *J*=10.3Hz, 1H), 3.76 (s, 3H), 3.77 (s, 3H), 3.93 (d, *J*=7.7Hz, 1H), 3.95-4.00 (m, 1H), 4.6 (t, *J*=7.7Hz, 1H), 5.04 (ddd, *J*=1.4, 5.0, 8.0Hz, 1H) 6.71 (dd, *J*=1.6, 8.0Hz, 1H). The structure of **16** was estimated by the observation of NOEs between 2β proton (δ 3.95-4.00) and 3β proton (δ 2.02), and between 3α proton (δ 1.74) and 4α proton (δ 3.10-3.15).

(*Received in Japan* 7 *May* 1996; *revised* 12 *June* 1996; *accepted* 17 *June* 1996)