CHEMISTRY LETTERS, pp. 1963-1966, 1989.

# A New Facile Method for Construction of β-Arylpyrrolidine Rings and Its Application to Synthesis of (±)-Mesembrine[1)]

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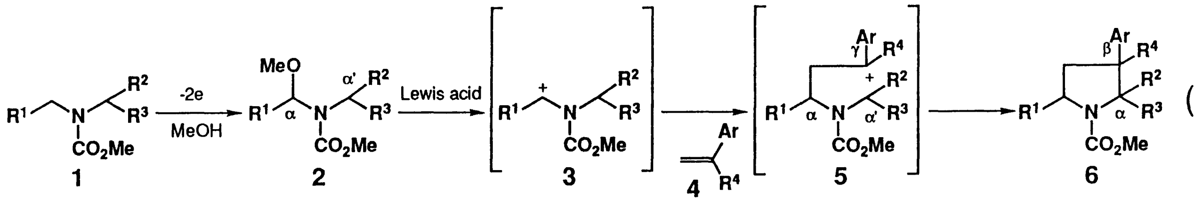
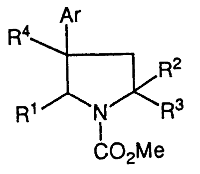
Lewis acid treatment of dimethyl N-methoxycarbonyl-N-methoxymethylaminomalonate together with aryl olefins afforded α,α,N-tris(methoxycarbonyl)-β-arylpyrrolidines, and one of the products was successfully converted to (±)-mesembrine.

Since the β-arylpyrrolidine skeleton is found in a variety of naturally occurring alkaloids such as mesembrine (14),[2)] it is worthwhile to exploit a new convenient method for constructing the skeleton.[3)] On the other hand, we have been extensively studying new synthetic methods of nitrogen heterocycles by using N-methoxycarbonyliminiumions (3) as key intermediates which are generated by acid treatment of α-methoxylated N-methoxycarbonylamines (2) prepared by anodic oxidation of carbamates (1).[4)] The key ions (3) seem to have high potentiality for the synthesis of β-arylpyrrolidine derivatives (6) through their reaction with aryl olefins (4), provided that the trapping of intermediate γ-cations (5) with the α'-carbon is made possible by contribution of suitable substituents $R^2$ and $R^3$ (Eq. 1).



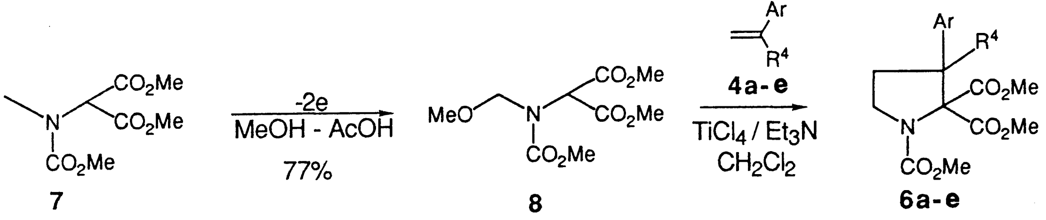
(1)

Examining a variety of functional groups for $R^2$ and $R^3$, we have found that a methoxycarbonyl group is suitable for the substituents $R^2$ and $R^3$. Thus, the reaction of dimethyl N-methoxycarbonyl-N-methoxymethylaminomalonate (8) (2; $R^1$=H and $R^2$=$R^3$=$CO_2Me$) with 4 afforded 6. The regioisomer 6' was not formed.



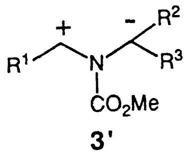
6'

The starting compound 8 was prepared by anodic oxidation of dimethyl N-methoxycarbonyl-N-methylaminomalonate (7) (40 mmol) in methanol (30 ml) containing acetic acid (3 ml) (77% yield at 9.4 *F*/mol).[5)] The reaction of 8 with 4 was carried out as follows: Under nitrogen atmosphere, a solution of 4 (2 mmol) and $Et_3N$ (1 mmol)[6)] in $CH_2Cl_2$ (5 ml) was added dropwise into a refluxing solution of 8 (1 mmol) and $TiCl_4$ (2 mmol) in $CH_2Cl_2$ (10 ml),[7)] and the resulting solution was refluxed for 1 h. Treatment of the reaction mixture with water[8)] followed by purification of the products by column chromatography gave the expected 6 in the yields shown in Eq. 2.[9,10)]



(2)

| | |
|---|---|
| a; Ar=3,4-dimethoxyphenyl, $R^4$=H | 87% |
| b; Ar=4-methoxyphenyl, $R^4$=H | 56% |
| c; Ar=phenyl, $R^4$=Me | 78% |
| d; Ar=phenyl, $R^4$=H | 83% |
| e; Ar=4-chlorophenyl, $R^4$=H | 71% |

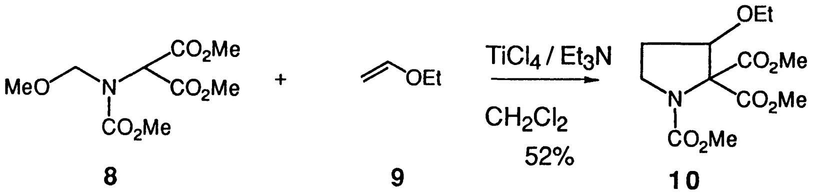


3'

Although the formation of 6 is undoubtedly explainable by a stepwise mechanism involving 3 as the intermediate as described in Eq. 1, a possibility of the formation of a betaine 3' followed by a concerted cycloaddition between 3' and 4 should be discussed since 3' possesses a structure similar to azomethine ylide which has been reported to add to olefins with a concerted mechanism and form pyrrolidine skeletons.[11)]

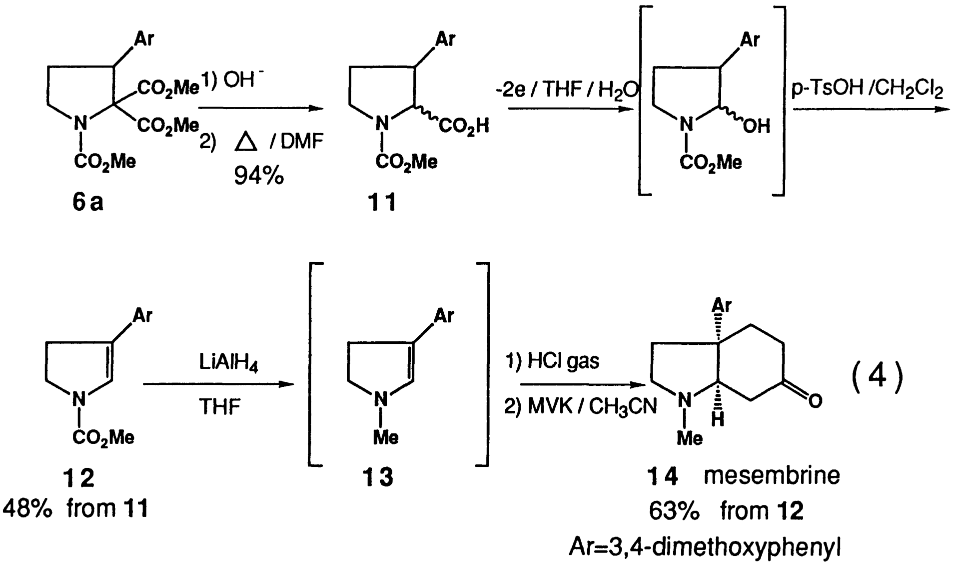
The intermediary formation of 3' is, however, unlikely on the basis of the following two points. Namely, (i) the reaction conditions containing Lewis acids do not seem to be suitable for the formation of 3' since it requires base induced abstraction of a proton from α'-position of 3, and (ii) the concerted cycloaddition reaction of stabilized[12)] or nonstabilized[13)] azomethine ylides with styrene has been known to be not regioselective, while high regioselectivity was observed in the formation of 6.

Ethyl vinyl ether (9) was also effective to this method instead of aryl olefins (Eq. 3).[14)]



(3)

One of the products, 6a was easily converted to (±)-14 (Eq. 4). Namely, hydrolysis of 6a and subsequent decarboxylation gave a proline derivative 11 (94% yield). Anodic oxidation of 11 in a mixed solvent of THF and water[16)] followed by acid treatment gave an enecarbamate (12) (48% yield), which was reduced with $LiAlH_4$ to give an enamine (13). The condensation of 13 with methyl vinyl ketone (MVK) afforded (±)-14 in 63% yield from 12.[10,17)]



(4)

One of the authors (Y.M.) thanks the Ministry of Education, Science and Culture, Japan, for a Grant-in-Aid for the Development Scientific Research (2) (No. 01850193).

## References

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2) P. W. Jeffs, "The Alkaloids," ed by R. H. F. Manske, Academic Press, New York (1981), Vol. XIX, pp. 1-80.

3) R. V. Stevens, Acc. Chem. Res., 10, 193 (1977); J. D. Winkler, C. L. Muller, and R. D. Scott, J. Am. Chem. Soc., 110, 4831 (1988).

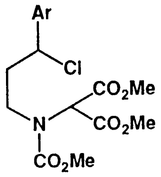
4) For example, see; T. Shono, Y. Matsumura, and K. Tsubata, Org. Synth., 63, 206 (1984).

5) The current efficiency decreased when acetic acid was not used; T. Shono, Y. Matsumura, O. Onomura, and Y. Yamada, Synthesis, 1987, 1099.

6) In the absence of $Et_3N$, polymerization of styrene preferentially occurred.

7) The starting compound 8 was recovered when the reaction was carried out without heating.

8) In the case of 4d,e, a mixture of 6 and the corresponding noncyclized chloride A was obtained, whereas workup with the reaction mixture with alkaline solution (NaOMe/MeOH) afforded only 6 in the yields shown in Eq. 2.



**A**

9) Polymers of aryl olefins were obtained as the by-products.

10) All new compounds gave satisfactory spectral and analytical data.

11) J. W. Lown, "1,3-Dipolar Cycloaddition Chemistry (General Heterocyclic Chemistry Series)," ed by A. Padwa, Wiley-Interscience, New York (1984), Vol. I, p. 653.

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14) The reaction of 8 with 1-octene gave not the expected compound (B) but a cyclic carbamate (C) in 34% yield.[15]

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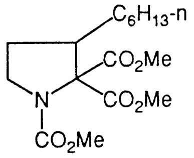
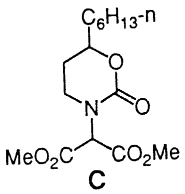
16) H. Horikawa, T. Iwasaki, K. Matsumoto, and M. Miyoshi, J. Org. Chem., 43, 335 (1978).

17) The condensation of 13 with methyl vinyl ketone leading to 14 has been known; R. G. Stevens and M. P. Wentland, J. Am. Chem. Soc., 90, 5580 (1968).



**B**



**C**

(Received August 8, 1989)