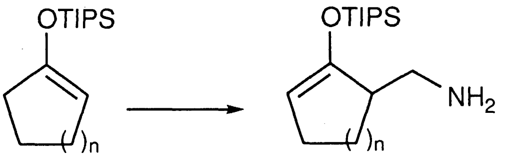
CHEMISTRY LETTERS, pp. 1655-1658, 1993.

# Construction of N-Acylated 4-Piperidones via Selective Carbon-Nitrogen and Carbon-Carbon Bond Formation

Mitsumasa TAKAHASHI, Keiji TANINO, and Isao KUWAJIMA*
Department of Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152

N-Acylated 4-piperidone was prepared in good overall yield through an initial formation of the imine from the reaction of α'-aminomethylated enol silyl ether with an aldehyde followed by cyclization effected with an acid anhydride. The latter cyclization reaction seems to proceed preferentially through a boat-like transition state to give the piperidone having *exo* substituent.

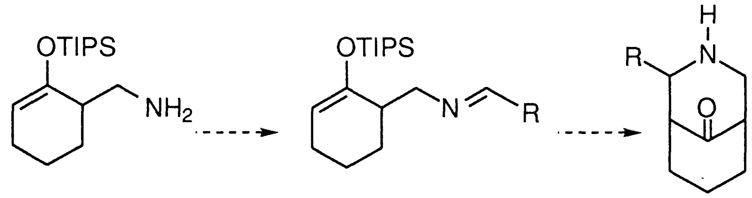
In connection with nitrogen-containing natural product synthesis, selective carbon-carbon as well as carbon-nitrogen bond formation reactions are important in organic synthesis.[1)] We recently reported a generation of Lewis acid activated N-silylated formaldimine which reacts with enol silyl ethers in an ene-like manner to afford α'-aminomethylated enol silyl ethers **1**.[2)]



(1)

**1**

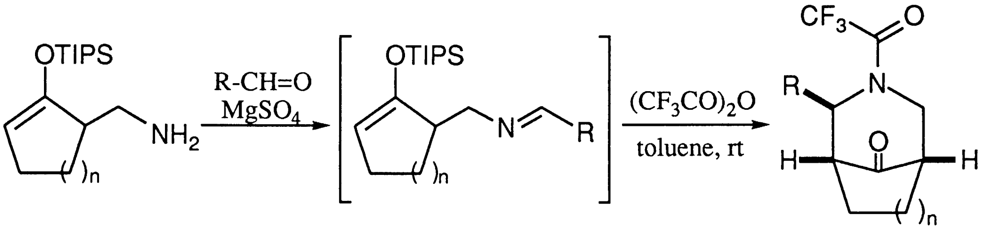
By utilizing these functional groups, we envisioned to explore a new methodology for the synthesis of 4-piperidone derivatives[3)] via successive formation of carbon-nitrogen and carbon-carbon bond formation as shown in Eq 2.



(2)

An initial conversion to the aldimine was performed by treating with the corresponding aldehyde in the presence of anhydrous $MgSO_4$: The enol moiety survived the reaction conditions to produce the imine in good yields. On attempts for the next cyclization, any Lewis acids did not give the satisfactory results: neither $BF_3 \cdot OEt_2$ nor $AlCl_3$ effected the cyclization, while use of $TiCl_4$ afforded the corresponding piperidone in only a trace amount. After several examinations, the desired transformation could be induced cleanly by using an acid anhydride or acyl chloride to activate the imine moiety and the products were obtained as the corresponding N-acylated piperidones in good overall yield from **1** (see the Table).

Except the entry e) (a diastereomeric ratio, 9:1), the products were usually obtained as the single diastereomers having *exo* substituent. However, they are mixtures of two atropisomers due to the restricted rotation around the amide group. The stereochemical feature of the product was typically assigned by NOE experiment of the compound **2b**$^{4)}$ (entry b) obtained from benzaldehyde.



**2**

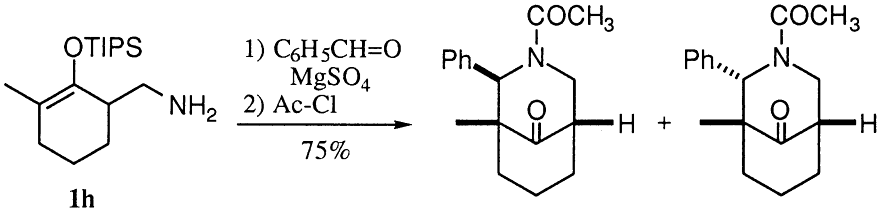
(3)

Table. Preparation of **2**

| Entry | n | R | Yield of **2** (%)$^{a)}$ |
|---|---|---|---|
| a | 1 | $C_6H_5$- | 61 |
| b | 2 | $C_6H_5$- | 79 |
| c | 2 | $(CH_3)_2CH$- | 84 |
| d | 2 | $C_6H_{13}$- | 33 |
| e | 2 | $C_6H_5CH=CH$- | 90 |
| f | 2 | EtO-CO- | 69 |
| g | 3 | $C_6H_5$- | 68 |

a) Isolated overall yield.

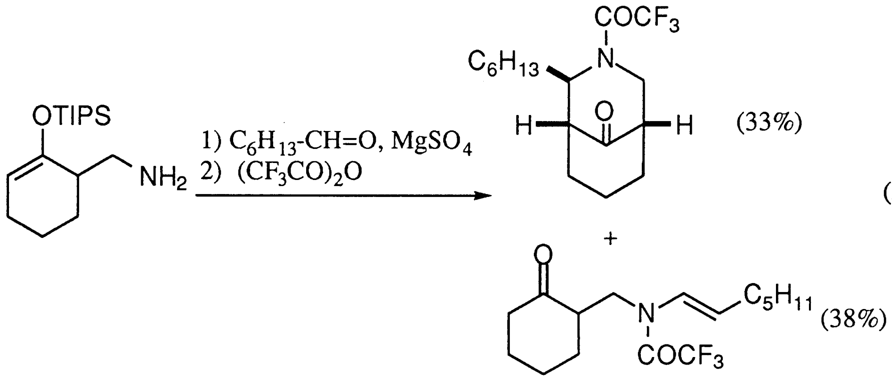
A substituted compound **1h** also gave the corresponding piperidone **2h** as a major product along with **2h'** (diastereomeric ratio = 10:1)$^{5)}$ (eq 4).



**1h** **2h** **2h'**

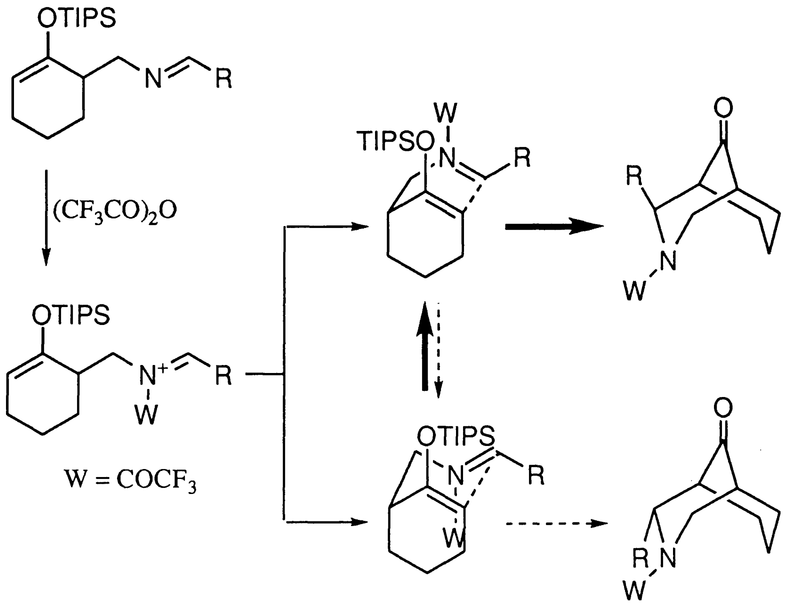
(4)

On using a straight-chained aliphatic aldehyde, the product yield decreased due to isomerization to the N-acylated enamine via deprotonation (entry d), but an α-branched aldehyde gave the piperidone in good yield (entry c).



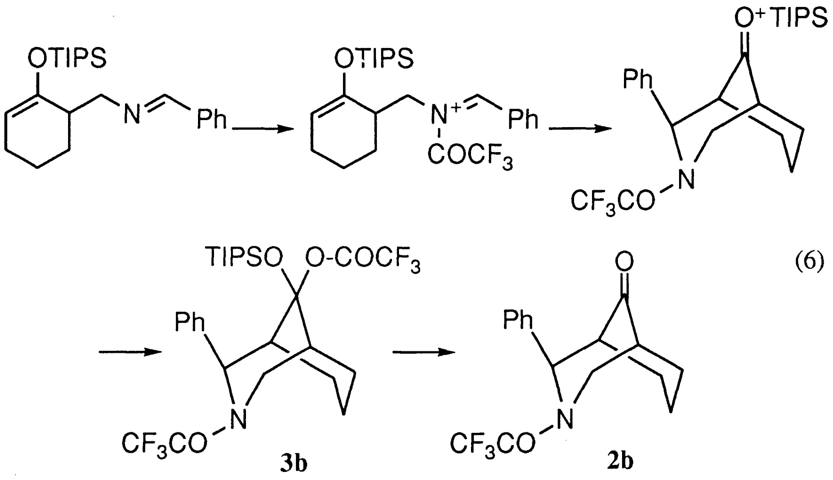
(5)

The piperidone cyclization may take place through either a chair- or boat-like transition state. Judging from the product obtained, the former may be greatly disfavored by severe steric repulsion between the ring carbons and N-substituent (and possibly the substituent R), and the reaction proceeds preferentially through the boat-like transition state to form the product having *exo* substituent.



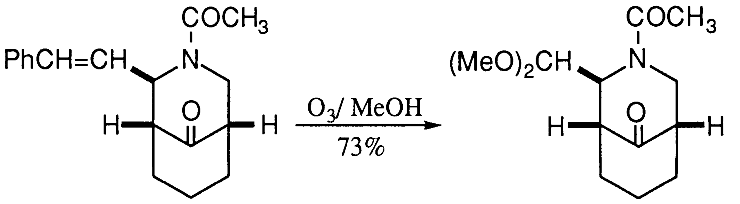
Scheme 1.

Monitoring the reaction (entry b) by NMR revealed a rapid disappearance of vinyl proton of enol ether, but the spectrum was completely different from that of the final product **2b**. After standing overnight at room temperature, complete conversion to **2b** was identified by $^1H$ NMR. Accordingly, an initial N-acylation and the subsequent cyclization appear to take place quite rapidly to form the intermediate **3b**,⁶⁾ from which silyl trifluoroacetate is slowly removed to yield the final product **2b**.



(6)

The present procedure seems to be quite useful for the preparation of various type piperidone derivative. For example, ozonolysis of the product (entry e) derived from cinnamaldehyde gave the corresponding acetal. Such highly functionalized compound may allow selective carbon chain elongation or introduction of functional groups to open a new aspect of piperidone chemistry.

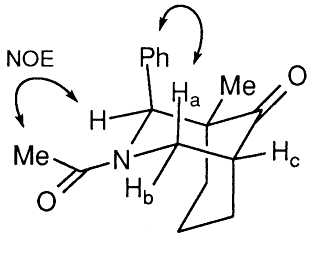


(7)

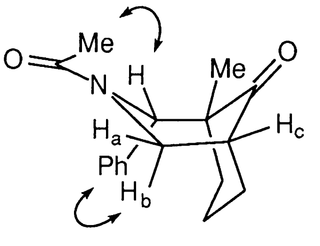
Acknowledgement. This work was partially supported by Grants from the Ministry of Education, Science, and Culture of the Japanese Government.

References

1) See, for example, L. E. Overman, *Acc. Chem. Res.*, **25**, 352 (1992).
2) K. Tanino, M. Takahashi, K. Murayama, and I. Kuwajima, *J. Org. Chem.*, **57**, 7009 (1992).
3) For the preparation of 3-azabicyclo[3.3.1]nonan-9-one derivatives, see, V. Baliah, R. Jeyaraman, and L. Chandrasekaran, *Chem. Rev.*, **84**, 379 (1983). H. O. House, P. P. Wickham, and H. C. Muller, *J. Am. Chem. Soc.*, **84**, 3139 (1962). However, these methods are only applicable to the synthesis of symmetrically substituted derivatives.
4) $^1$H NMR (270 MHz, $CDCl_3$) of each atropisomer of **2b**: δ 3.17 (d, $J$ = 17.2 Hz, 1H, $C\underline{H}_2$-N), 4.35 (d, $J$ = 17.2 Hz, 1H, $C\underline{H}_2$-N), 6.65 (br s, 1H, $C\underline{H}$-N). δ 3.47 (d, $J$ = 16.0 Hz, 1H, $C\underline{H}_2$-N), 3.91 (d, $J$ = 16.0 Hz, 1H, $C\underline{H}_2$-N), and methyne proton ($C\underline{H}$-N) could not be detected due to the overlap with the aromatic protons. NOE was observed between aromatic protons and $CH_2$-N proton appeared at higher field in each case, but not between $CH_2$-N and CH-N proton. These results support the structure of **2b**.
5) The major and minor products, **2h** and **2h'**, were determined by the following NOE and coupling constants.



$J_{ac} = 4$ Hz, $J_{bc} = 0$ Hz



$J_{ac} = 11$ Hz, $J_{bc} = 3$ Hz

6) On quenching the reaction mixture at an early stage, the formation of **3b** was detected. Methylene protons ($CH_2$-N) appear as follows: $^1$H NMR (270 MHz, $CDCl_3$) δ 4.26 (d, $J$ = 8.0 Hz, 1H) and 4.52 (d, $J$ = 8.0 Hz, 1H).

( Received June 18, 1993 )