the formation of the photocycloaddition–reto-Mannich product **20**, in 74% yield. Methylation with trimethyloxonium tetrafluoroborate followed by treatment with 4-dimethylaminopyridine in reluxing acetonitrile produced mesembrine, **5**, in 84%g yield, identical (^{1}H NMR, IR, MS) with an authentic sample.[15]

This efficient synthesis of the alkaloid mesembrine (seven steps, 33% overall yield) illustrates the utility of the vinylogous amide photocycloaddition–retro-Mannich–Mannich sequence. The application of this methodology to the construction of more complex alkaloids is currently in progress in our laboratory and will be reported in due course.

Acknowledgment. Support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Institutes of Health (CA40250 and KO4-CA01337), and training grants to C.L.M. (GM 07183) and R.D.S. (PHS-5T32-GM-07281), and American Cancer Society Institutional Grant, the Alfred P. Sloan Foundation, and Merck, Sharp and Dohme is gratefully acknowledged. The NMR instruments used were funded in part by the NSF Chemical Instrumentation Program and by the NCI via the University of Chicago Cancer Research Center (CA 14599).

Registry No. (±)-**5**, 6023-73-0; **6**, 114634-41-2; **7**, 114634-44-5; (±)-**10**, 114634-42-3; (±)-**11**, 114634-45-6; **13**, 67175-84-2; **13** (DNP derivative), 114634-46-7; (±)-**14**, 114634-43-4; **15**, 105174-63-8; **16**, 114634-47-8; **17**, 114634-48-9; **18**, 114634-49-0; (±)-**20**, 114634-50-3; $ClCO(CH_2)_2Br$, 15486-96-1; $ClCH{=}CHCOOCH_3$, 7119-27-9; veratrole, 91-16-7.

Supplementary Material Available: Spectral data for **15–20** (1 page). Ordering information is given on any current masthead page.

(15) We thank Professors Albert Meyers (Colorado State University) and Stephen Martin (University of Texas at Austin) for generously providing authentic samples of mesembrine.

On the Tautomerism of Dihydropyrimidines: The Influence of the 2- and 5-Substituents on the Observation of Tautomers[1]

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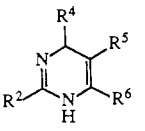
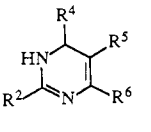
Tautomerism in the dihydropyrimidine system has not been sufficiently investigated to date. The location of the tautomeric double bond is not clearly indicated in most papers. Namely, the tautomeric compounds were drawn as either tautomer **a** or **b** or as an unspecified form without sufficient investigation.[3]

We recently carried out the X-ray crystallographic analysis of 4-(2-chlorophenyl)-5-(ethoxycarbonyl)-2,6-dimethyldihydropyrimidine and found it to exist as the 1,4-dihydro form **a** in the crystalline state.[4] Regarding the dihydro form in solution, Van der Plas et al.[5] and Girke[6] independently studied the behavior of a variety of dihydropyrimidines. They attempted to obtain the NMR spectra in deuteriochloroform ($CDCl_3$) of each of the tautomers (type a and type b), but even at temperature below 0 °C this was not possible. Weis carefully studied the tautomerism

Chart I



a



b

	R^2	R^4	R^5	R^6
1	CF_3	2-NO_2-C_6H_4	COOiPr	CH_3
2	SMe	2-NO_2-C_6H_4	COOiPr	CH_3
3	NMe_2	2-NO_2-C_6H_4	COOiPr	CH_3
4	H	2-NO_2-C_6H_4	COOiPr	CH_3
5	Me	2-NO_2-C_6H_4	COOiPr	CH_3
6	iPr	2-NO_2-C_6H_4	COOiPr	CH_3

of 4-methyl-2,6-diphenyldihydropyrimidine and observed two individual tautomers (type a and type b) at −50 °C in a dilute $CDCl_3$ solution (0.001–0.003 M).[7]

Recently, Kashima observed the tautomeric equilibrium between dihydropyrimidines in the 2-(dimethylamino)-4,6,6-trimethyldihydropyrimidine system. However, in the proton NMR experiment the location of the tautomeric double bonds could not be clearly determined.[8] We synthesized a variety of 2-substituted-5-(alkoxycarbonyl)-4-(2-nitrophenyl)-6-methyldihydropyrimidines but usually observed an averaged broad NMR (270 MHz) spectrum, as the rate of proton transfer from one nitrogen to the other was very fast in most solvents (especially in $CDCl_3$) at ambient temperature (25 °C). However, we succeeded in observing two individual tautomers with compounds **1** and **2** at ambient temperature even in a highly concentrated $CDCl_3$ solution as well as in C_6D_6 as shown below.

Because a substituent at position-2 should have an influence on the electron densities of the *N*-1, *C*-2, *N*-3 system, we expected that this substituent would affect the tautomeric equilibrium. Moreover, we supposed that the ester group at position-5 may have a role in affecting the tautomerism. Thus, compounds with six different substituents at position-2 (X = CF_3, SMe, NMe_2, H, Me, and *i*-Pr) were synthesized.[9] In the case of compounds **4**, **5**, and **6**, we could not observe tautomers by NMR (100–360 MHz, $CDCl_3$, 25 °C), but the averaged spectra were obtained instead. It is of interest that two distinct tautomers **a** and **b** were successfully observed at ambient temperature in $CDCl_3$ with compounds **1** and **2**. This finding means that the rate of proton exchange in the dihydropyrimidine system is sometimes very slow on the NMR time scale (100–270 MHz).

The equilibrium constants k can be calculated from the data obtained from the NMR measurement. Generally, if there are two tautomers A and B in solution as shown in Scheme I, the equilibrium constants k_A and T_{1A} can be calculated from the simultaneous eq 2. In a similar manner, k_B and T_{1B} can be obtained.[10]

Scheme I[a]

$$[A] \underset{k_B}{\overset{k_A}{\rightleftharpoons}} [B] \qquad k_A[A] = k_B[B] \tag{1}$$

$$M_A/M_{0A} = 1/(1 + k_A T_{1A}) \qquad 1/T_{1Aeff} = 1/T_{1A} + k_A \tag{2}$$

[a] [A], concentration of tautomer **a**; [B], concentration of tautomer **b**; M_A/M_{0A}, ratio of remaining magnetization under saturation transfer conditions; T_{1Aeff}, observable longitudinal relaxation time; T_{1A}, theoretical longitudinal relaxation time.

(1) Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.
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(9) All compounds have satisfactory spectral data: IR, NMR, MS, and Anal. NMR spectra were recorded by JEOL FX-100 (100 MHz), JEOL GX-270 (270 MHz), Nicolet NT-360 (360 MHz), and GE GN-500 (500 MHz) with TMS as the internal standard.
(10) Gadian, D. G. *Nuclear Magnetic Resonance and Its Applications to Living Systems*; Oxford University Press: New York, 1982.

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Table I. The Equilibrium Constants k of the Tautomerism (500 MHz, in C_6D_6)

no.	X	concn (M)	ratio of tautomers	T_{1Aeff} (s)	T_{1Beff} (s)	M_A/M_{0A}	M_B/M_{0B}	k_A (s^{-1})	k_B (s^{-1})	k_B/k_A
1	CF_3	0.027	a:b = 2.17:1.00	1.05	0.75	0.56	0.33	0.42	0.88	2.10
		0.123	a:b = 2.94:1.00	0.65	0.43	0.47	0.21	0.81	1.85	2.28
2	SMe	0.030	a:b = 1.00:1.15	0.43	0.52	0.27	0.27	1.69	1.41	0.83

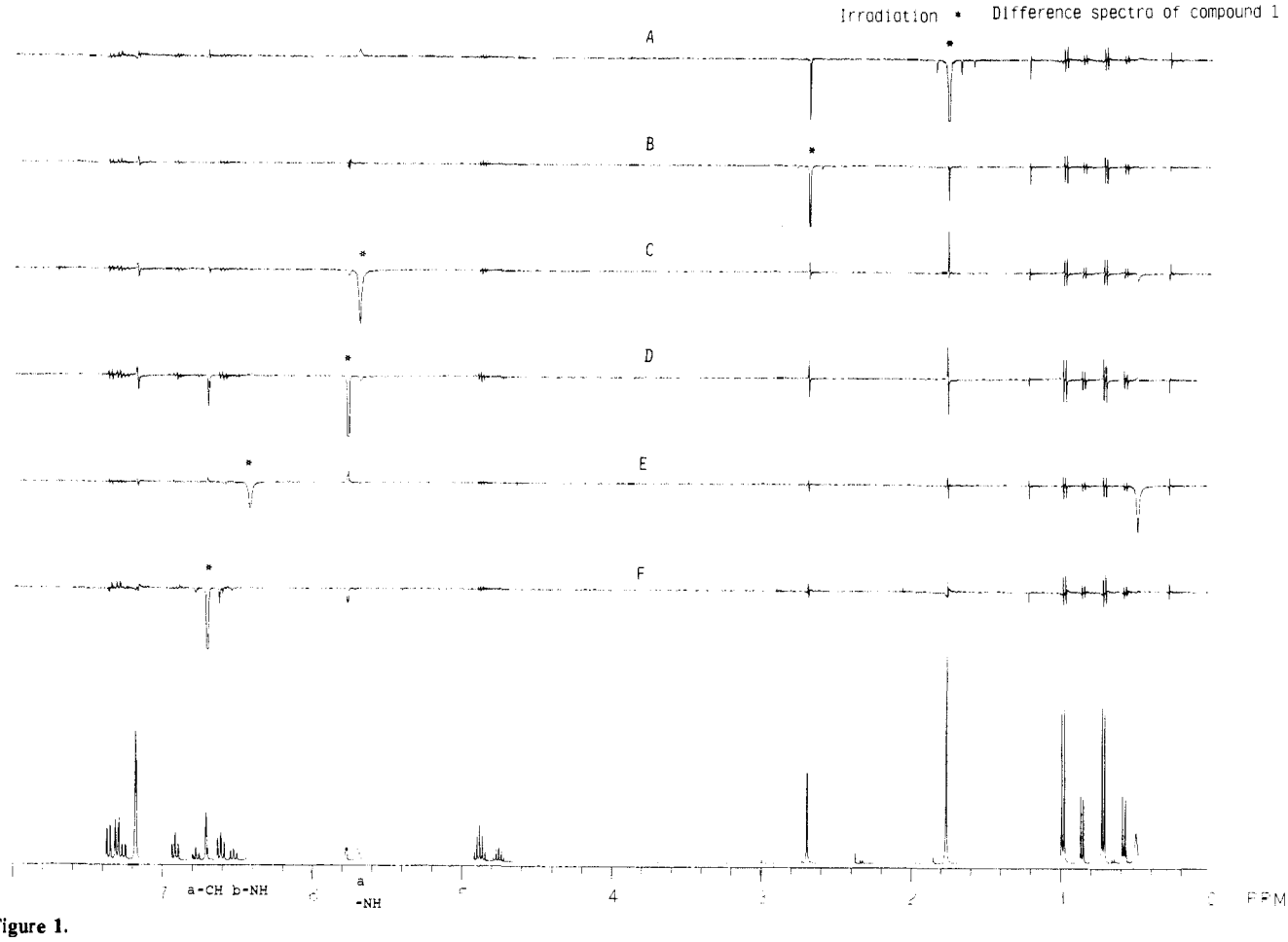

Figure 1.

The technique used to calculate these constants involves selectively perturbing the magnetization of one site with a weak saturating field and then measuring the T_{1Aeff} value of the other site by the inversion recovery method. The value of M_A/M_{0A} can be obtained by comparison of the steady-state intensity with a saturated field and a nonsaturated field. Thus, the equilibrium constants k_A and k_B were obtained by solving the simultaneous eq 2 (see Table I).

In order to confirm that the two compounds are definitely tautomers, NMR studies with compound **1** were undertaken in C_6D_6 by using a selective saturation technique (see the difference spectra A–F).

By irradiation at the NH proton (spectrum E), a NOE (7.6%) was observed between this proton and the methine proton (δ 5.78, 1 H, d, J = 2.5 Hz), while irradiation at the NH proton (spectrum C) produced a NOE (1.3%) at the 6-methyl protons (δ 1.78, 3 H, s). By irradiation of the methine proton of **1a**, a saturation transfer was observed to the methine proton of **1b** (spectrum F). This means that the NH proton is slowly transfered from position-1 to position-3. Conversely, a saturation transfer was observed from **1b** to **1a** (spectrum D). The saturation transfer was recorded with the methyl signals at position-6 (spectrum A and B). This proves that the two compounds are tautomers. The ratio of **1a**/**1b** or **2a**/**2b** is apparently dependent upon the concentration and the temperature of the solution (see Supplementary Material, Table II). Interestingly, the ratio of **1a** to **1b** gradually goes up due to intermolecular proton exchange as the solution becomes concentrated, and when the solution is warmed up the ratio of tautomer **b** to **a** gradually increased, but the NMR spectrum did not change into an averaged spectrum. Consequently, the 1,4-dihydro form **a** seems to be more stable than the 3,4-dihydro form **b** in solution.

This is the first observation that the presence of the electron-withdrawing groups (CF_3) at the position-2 of dihydropyrimidines causes proton exchange to become very slow such that the individual tautomers could be detected by 100–360 MHz NMR spectra at ambient temperature. This may be due to an electron deficiency of the *N*-1, *C*-2, *N*-3 system. Similar results were obtained with compound **2**. In this case the major tautomer is **2b**, and the NMR spectrum became broad at high concentrations (0.172 M).

Namely, the ratio of **2b** to **2a** proportionally increases with the temperature and the concentration. The SMe group has not only a weak electron-donating effect (+M effect) but also is electron withdrawing due to the contribution of the d orbitals of the S atom. This may be the reason that compound **2** behaves differently from compound **3** having electron-donating groups and exists as two detectable tautomers.

On the contrary, compound **3** exists exclusively in the 3,4-dihydro form **b** as indicated by the coupling constant (J = 3.3 Hz) of **3** which is larger than that of **1b** (J = 2.5 Hz) or that of **2b** (J = 3.0–3.2 Hz).

The reason that only tautomer **b** was observed seems to be due to resonance stabilization effects (i.e., the interaction of the conjugated double bonds with the lone pair of the electron-donating group (NMe_2) and the influence of the electron-withdrawing ester group at position-5). In the other cases (H and alkyl), it is not

easy to observe tautomers at ambient temperature. In compound **5** we could not observe them in $CDCl_3$ even at −50 °C.

Therefore, the electronic effects of the substituents at position-2 and -5 of the dihydropyrimidine ring play important roles in making possible the observation of individual tautomers.

These findings will facilitate recognition of tautomerism in other dihydropyrimidine derivatives and may serve as a foundation for the investigations of tautomerism of other heterocyclic amidines.

Registry No. 1a, 114790-88-4; **1b**, 114790-93-1; **2a**, 114790-89-5; **2b**, 114790-94-2; **3b**, 114790-90-8; **4a**, 114790-91-9; **5a**, 101645-67-4; **6a**, 114790-92-0.

Supplementary Material Available: Table II (tautomerism of 2-substituted dihydropyrimidine derivatives on the different solvents, concentrations, and temperature) and synthetic methods for compounds **1–6** (5 pages). Ordering information is given on any current masthead page.

Effects of BF_3·Et_2O on Higher Order Organocuprate Reactions: Substrate Activation or Cuprate Modification?†

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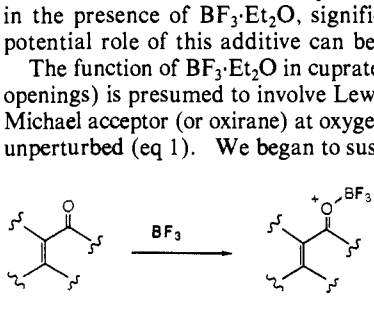
In spite of the vast number of successful applications of organocuprates to synthetic schemes which call for conjugate addition reactions,[2] there are many times when results obtained are simply not satisfactory. Whether due to steric hindrance in the substrate or limited reagent stability or reactivity, cuprate formation by itself does not imply success in subsequent Michael additions. To improve the chances for effecting the desired coupling, it is now common practice to admix either lower order (L.O.) or higher order (H.O.) cuprates[3] with an additive such as BF_3·Et_2O[4] or Me_3SiCl,[5] which oftentimes leads to spectacular increases in rates and yields of reactions. Just how these species effect the solution chemistry of this substrate/reagent combination, however, is still an open matter. We now report that by carrying out both chemical and NMR spectral studies on H.O. cuprates in the presence of BF_3·Et_2O, significant insight regarding the potential role of this additive can be realized.

The function of BF_3·Et_2O in cuprate 1,4-additions (and epoxide openings) is presumed to involve Lewis acid complexation of the Michael acceptor (or oxirane) at oxygen, while the cuprate remains unperturbed (eq 1). We began to suspect that this is not the full

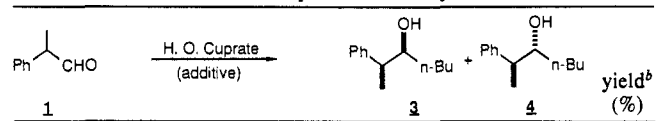


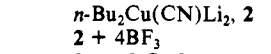
(1)

story, if correct at all, when we examined the 1,2-addition of $Bu_2Cu(CN)Li_2$ (**2**) to aldehyde **1**[6a] under the influence of various additives (see Table I).[6b] The adduct is expected to form a mixture of syn **3** and anti **4** products, providing an internal stereochemical label. As summarized in Table I, although **2** reacts slowly with **1** at −78 °C, an equal amount of **3** and **4** is formed. The same is true for reactions of **2** in the presence of excess BF_3. However, while **2** is totally unreactive (even at room temperature) in the presence of 15-crown-5-ether, the addition of BF_3 to this mixture at −78 °C not only restores activity but also leads to a substantially improved ratio of diastereomers (ca. 10:1 syn:anti by capillary GC).[6b] Moreover, the most reactive reagent combination is in fact the one containing the unreactive cuprate and crown ether, plus BF_3, which consumes aldehyde somewhat faster than does the reactive **2** plus BF_3. Identical results could be obtained by placing the Li^+ sequestering crown ether effect within the cuprate itself by using an acetylenic ligand,[7] as in **5**. That these observations are not consistent with simple carbonyl activation was further strengthened by precomplexing **1** with BF_3 followed by exposure to **5**, which does not give the previously noted 10:1 ratio (see Table I).

To ascertain how the BF_3 must effect the cuprate we turned to low-temperature, high field NMR. H.O. cuprates $Me_2Cu(CN)Li_2$ (**6**), $Me(MeOC(CH_3)_2C{\equiv}C)$-$Cu(CN)Li_2$ (**7**),[8] and Me(2-thienyl)$Cu(CN)Li_2$ (**8**)[8] were studied. Addition of BF_3·Et_2O (2 equiv) to **6** at −90 °C immediately leads to the appearance of

Table I. Addition of H. O. Cuprates to Aldehyde **1**[a]



1	3	4	yield[b] (%)
n-$Bu_2Cu(CN)Li_2$, **2**	1	1	52–72
2 + $4BF_3$	1.3	1	55–65
2 + 15-Cr-5	no reaction		
2 + 15-Cr-5 + $4BF_3$	8–10	1	quant
 **5**	no reaction		
5 + $4BF_3$	10–12	1	70
1 + $4BF_3$, then **5**	3	1	20–30
n-Bu(2-Th)$Cu(CN)Li_2$ + $4BF_3$	4	1	50
n-$BuCu(CN)Li$ + $4BF_3$	3.5	1	55
n-$BuLi{\cdot}2BF_3$	2	1	40

[a] All reactions were run in THF containing 2 equiv of cuprate at −78 °C over a 3-h period. [b] Yields (and ratios of diastereomers) were determined on the crude reaction mixtures by quantitative capillary GC. The remaining mass consisted mostly of starting aldehyde.

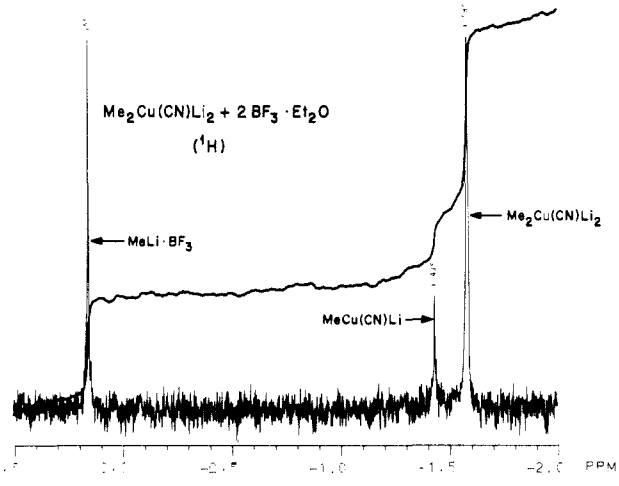


Figure 1. Proton NMR spectrum of $Me_2Cu(CN)Li_2$ + $2BF_3$·Et_2O in THF at −92 °C.

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

(1) A. P. Sloan Fellow, 1984–1988; Dreyfus Teacher-Scholar, 1984–1989.

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(3) For a review, see: Lipshutz, B. H. *Synth.* **1987**, 325.

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(6) (a) The 1,2-addition of cuprates to aldehydes was first noted by Posner: Posner, G. H.; Whitten, C. E.; McFarland, P. E. *J. Am. Chem. Soc.* **1972**, *94*, 5106. (b) Yamamoto, Y.; Maruyama, K. *Ibid.* **1985**, *107*, 6411.

(7) Corey, E. J.; Floyd, D. M.; Lipshutz, B. H. *J. Org. Chem.* **1978**, *43*, 3418.

(8) All information regarding this species is in the Supplementary Material.

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