

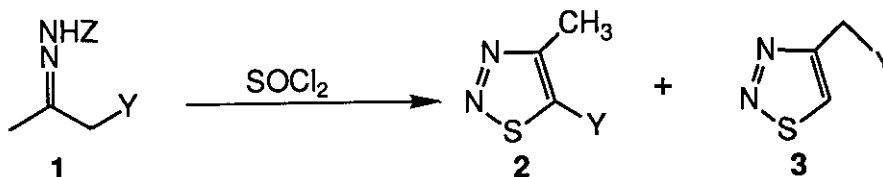
ON THE REGIOSELECTIVITY IN THE HURD-MORI REACTION

Mikako Fujita, Takeo Kobori,* Tamejiro Hiyama,[§] and Kiyosi Kondo

Sagami Chemical Research Center, 4-4-1 Nishiohnuma, Sagamihara, Kanagawa 229, Japan




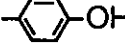
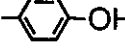
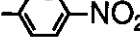


Abstract - Various α -substituted (Y) acetone hydrazones were subjected to the Hurd-Mori reaction to give the 4-methyl-5-Y-substituted 1,2,3-thiadiazoles and/or 4-Y-CH₂ derivatives. The ratio of the two products changed drastically depending on the kind of the substituent Y and was parallel to the relative rate of enolization of the two α -carbons in the parent ketones.

Because the Hurd-Mori reaction¹ is extremely convenient for construction of 1,2,3-thiadiazole ring, this reaction has been applied to the synthesis of many biologically active compounds by us² and others.^{3,4} The regioselectivity in the reaction of some mono substituted acetone hydrazones (1) has been examined. In general, 4-methyl-5-substituted (Y) products (2) result predominantly from substrates (1) (Y = *n*-alkyl, C₂H₅OCO, Ph, or Cl).^{4,5} To define the scope and limitation of the Hurd-Mori reaction, we also have studied the reaction of 1 having a wide variety of substituent Y. Herein we report that the regioselectivity changed depending on the kind of Y, and regioisomers (3) could be produced almost exclusively in certain cases.



[§] Present address: Research Laboratory of Resources Utilization, Tokyo Institute of Technology, 4255 Nagatsuta, Midori-ku, Yokohama, Kanagawa 227, Japan.

Table 1. The Hurd-Mori Reaction of Mono Substituted Acetone Hydrazone (1)

Entry	Y	Z	Combined yield (%) of 2 and 3	Ratio of 2 : 3
1	CH ₃	Tos	95 ^{a)}	80 : 20 ^{a,b)}
2	CH ₂ CH ₃	Tos	92	67 : 33 ^{c)}
3	CH(CH ₃) ₂	CO ₂ C ₂ H ₅	73	15 : 85 ^{a)}
4	CH(CH ₃) ₂	Tos	93	33 : 67
5	C(CH ₃) ₃	CO ₂ C ₂ H ₅	86	0 : 100
6	C(CH ₃) ₃	Tos	94	0 : 100
7	CH ₂ - 	Tos	87	67 : 33
8	N(CH ₃) ₂	CO ₂ C ₂ H ₅	73	0 : 100
9	O- 	CO ₂ C ₂ H ₅	53	81 : 19
10	O- 	Tos	55	87 : 13
11	O- 	CO ₂ C ₂ H ₅	66	85 : 15
12	O- 	Tos	52	88 : 12
13	O- 	CO ₂ C ₂ H ₅	51	65 : 35
14	S- 	CO ₂ C ₂ H ₅	94	98 : 2
15	S- 	Tos	78	97 : 3
16	SCH ₃	CO ₂ C ₂ H ₅	87	99 : 1
17	Cl	CO ₂ C ₂ H ₅	92 ^{a)}	90 : 10 ^{a)}
18	Br	CO ₂ C ₂ H ₅	85 ^{a)}	86 : 14 ^{a)}
19	F	CO ₂ C ₂ H ₅	83 ^{a)}	20 : 80 ^{a)}

a) Determined by ¹H nmr spectroscopy.

b) The ratio of 90 : 10 has been reported in Ref. 4.

c) The ratio reported in Ref. 5 is 75 : 25.

Hydrazones (1) were treated with 3 molar equiv. of thionyl chloride at room temperature. For example, 4,4-dimethyl-2-pentanone *N*-ethoxycarbonylhydrazone (0.77 g, 3.9 mmol) and thionyl chloride (0.84 ml, 11.6 mmol) in 1,2-dichloroethane (6.1 ml) were mixed at room temperature and stirred for 1 day. The mixture was neutralized with aqueous NaHCO₃ and worked up. Purification by silica gel column chromatography afforded 4-(2,2-dimethylpropyl)-1,2,3-thiadiazole (0.52 g, 86% yield).

The reaction was applied to various hydrazones (1), and the results are summarized in Table 1.⁶ As can be seen, thiadiazoles (2) and/or (3) were obtained in moderate to high yields. In the cases of Y = ArO, PhS, CH₃S, Cl, and Br, 4-methyl-5-substituted products (2) were produced preferentially (Entries 9-18) as usual. In contrast, those having an alkyl group for Y afforded unusual regioisomers (3) predominantly in the order of CH₃ < CH₂CH₃ and PhCH₂ < CH(CH₃)₂ (Entries 1-4 and 7). In particular, hydrazones (1) where Y = C(CH₃)₃ produced 3 as a sole product (Entries 5 and 6). In addition, dimethylamino and fluoro groups favored the formation of 3 (Entries 8 and 19).

We found that the selectivity (3/(2+3)) was parallel to the relative rate constant ($k_b/(k_a+k_b)$) of acid-catalyzed enolization of two α -carbons in the corresponding mono substituted acetones 4 (Figure 1).^{7,8}

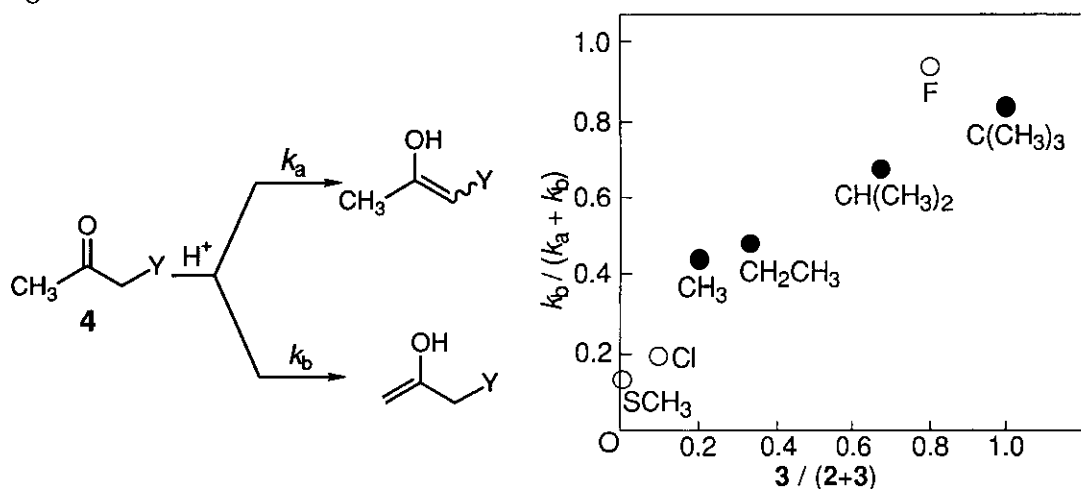


Figure 1. The ratio of 3/(2+3) vs. $k_b/(k_a+k_b)$ (●: Ref. 7, ○: Ref. 8; Substituent Y is shown).

Based on these observations, the regioselectivity of the Hurd-Mori reaction of acetone hydrazones with a substituent other than those tested will be estimated. As 1,2,3-thiadiazole ring is often employed as a key part of biologically active compound, the findings described here should be informative for the synthesis of 1,2,3-thiadiazoles of the desired type.

REFERENCES

1. C. D. Hurd and R. I. Mori, *J. Am. Chem. Soc.*, 1955, **77**, 5359
2. T. Kobori, M. Fujita, T. Hiyama, and K. Kondo, *Synlett*, 1992, 95; T. Kobori and D. Tsunemoto, *Eur. Pat. Appl.*, 1989, 335, 390 [*Chem. Abstr.*, 1991, **114**, 61829w].
3. For example, W. V. Curran, M. L. Sassiver, J. H. Boothe, and L. Jacob, *J. Heterocycl. Chem.*, 1985, **22**, 479; V. J. Lee, W. V. Curran, T. F. Fields, and K. Learn, *ibid.*, 1988, **25**, 1873; J. A. Lowe, III, T. F. Seeger, A. A. Nagel, H. R. Howard, P. A. Seymour, J. H. Heym, F. E. Ewing, M. E. Newman, A. W. Schmidt, J. S. Furman, L. A. Vincent, P. R. Maloney, G. L. Robinson, L. S. Reynolds, and F. J. Vinick, *J. Med. Chem.*, 1991, **34**, 1860.
4. E. W. Thomas, E. E. Nishizawa, D. C. Zimmermann, and D. J. Williams, *J. Med. Chem.*, 1985, **28**, 442.
5. O. Zimmer and H. Meier, *Chem. Ber.*, 1981, **114**, 2938.
6. Hydrazones (**1**) ($Z = \text{CO}_2\text{C}_2\text{H}_5$, $Y = \text{CH}_3$, CH_2CH_3 , or CH_2Ph) afforded only **3** in 14-30% yields, and **1** ($Z = \text{CO}_2\text{C}_2\text{H}_5$ or Tos, $Y = \text{OCH}_3$) also gave **3** as a sole isolable product but in 6-10% yields.
7. C. Rappe and W. H. Sachs, *J. Org. Chem.*, 1967, **32**, 3700.
8. J. Jullien and N-T-Lai, *Bull. Soc. Chim. Fr.*, 1970, 3948.

Received, 12th August, 1992