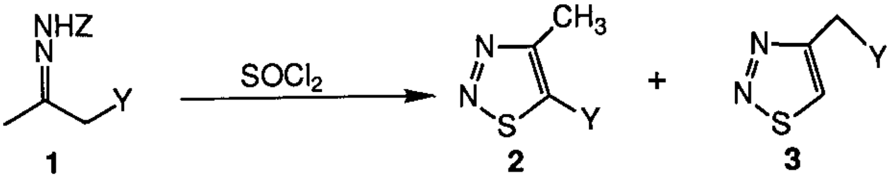
# *ON THE REGIOSELECTIVITY IN THE HURD-MORI REACTION*

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-$CH_2$ 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.

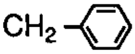
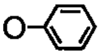
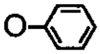
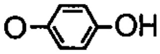
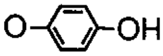
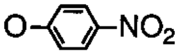
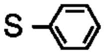
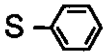
Because the Hurd-Mori reaction[1] is *extremely convenient for construction of 1,2,3-thiadiazole* ring, this reaction has been applied to the synthesis of many biologically active compounds by us[2] and others.[3,4] The regioselectivity in the reaction of some mono substituted acetone hydrazones (**1**) has been examined. In general, 4-methyl-5-substituted (Y) products (**2**) result predominantly from substrates (**1**) (Y = *n*-alkyl, $C_2H_5OCO$, 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 | $CH_2CH_3$ | Tos | 92 | 67 : 33[c)] |
| 3 | $CH(CH_3)_2$ | $CO_2C_2H_5$ | 73 | 15 : 85[a)] |
| 4 | $CH(CH_3)_2$ | Tos | 93 | 33 : 67 |
| 5 | $C(CH_3)_3$ | $CO_2C_2H_5$ | 86 | 0 : 100 |
| 6 | $C(CH_3)_3$ | Tos | 94 | 0 : 100 |
| 7 |  | Tos | 87 | 67 : 33 |
| 8 | $N(CH_3)_2$ | $CO_2C_2H_5$ | 73 | 0 : 100 |
| 9 |  | $CO_2C_2H_5$ | 53 | 81 : 19 |
| 10 |  | Tos | 55 | 87 : 13 |
| 11 |  | $CO_2C_2H_5$ | 66 | 85 : 15 |
| 12 |  | Tos | 52 | 88 : 12 |
| 13 |  | $CO_2C_2H_5$ | 51 | 65 : 35 |
| 14 |  | $CO_2C_2H_5$ | 94 | 98 : 2 |
| 15 |  | Tos | 78 | 97 : 3 |
| 16 | $SCH_3$ | $CO_2C_2H_5$ | 87 | 99 : 1 |
| 17 | Cl | $CO_2C_2H_5$ | 92[a)] | 90 : 10[a)] |
| 18 | Br | $CO_2C_2H_5$ | 85[a)] | 86 : 14[a)] |
| 19 | F | $CO_2C_2H_5$ | 83[a)] | 20 : 80[a)] |

a) Determined by $^1H$ nmr spectroscopy.

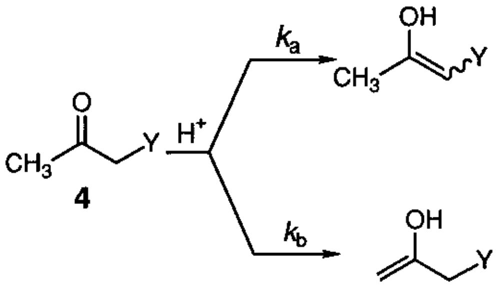
b) The ratio of 90 : 10 has been reported in Ref. 4.

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 $NaHCO_3$ 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, $CH_3S$, 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 $CH_3 < CH_2CH_3$ and $PhCH_2 < CH(CH_3)_2$ (Entries 1-4 and 7). In particular, hydrazones (**1**) where Y = $C(CH)_3$ 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]



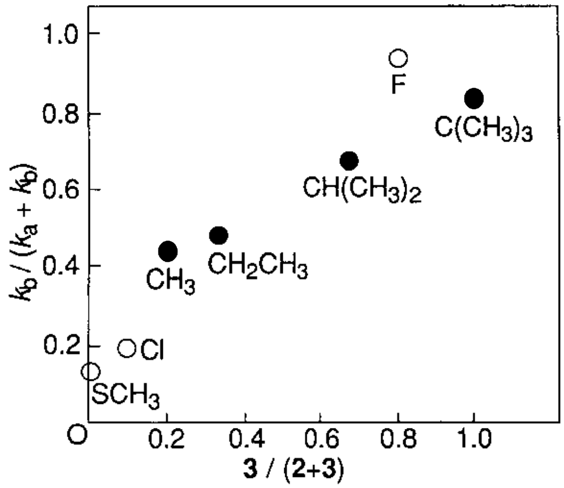


Figure 1. The ratio of **3**/(**2**+**3**) vs. $k_b/(k_a+k_b)$ (●: Ref. 7,○: Ref. 8; Substituent Y is shown).

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 = $CO_2C_2H_5$, Y = $CH_3$, $CH_2CH_3$, or $CH_2Ph$) afforded only **3** in 14-30% yields, and **1** (Z = $CO_2C_2H_5$ or Tos, Y = $OCH_3$) 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