

PREPARATION OF DEUTERIATED SUCCINIC ACIDS

Masashi Tashiro,^{a*} Hirohisa Tsuzuki,^a Shin-ichiro Isobe,^c
Hideyuki Goto,^b Shoji Ogasahara,^b Shuntaro Mataka,^a and
Tadashi Yonemitsu^c

^aInstitute of Advanced Material Study, Kyushu University, and

^bDepartment of Molecular Science and Technology, and
Graduate School of Engineering Sciences, Kyushu University,
6-1, Kasuga-koh-en, Kasuga-shi, Fukuoka 816, Japan

^cDepartment of Industrial Chemistry, Faculty of Engineering,
Kyushu Sangyo University, 2-327, Matsukadai, Kashi-i,
Higashi-ku, Fukuoka-shi, Fukuoka 813, Japan

SUMMARY

Succinic [2,3-²H₂]- and [2,2,3,3-²H₄]-acids were prepared from maleic anhydride and dimethyl fumarate, and acetylene dicarboxylic acid and its dimethyl ester by treatment with Cu-Al and Ni-Al alloys in 10% NaOD-D₂O in 95% to 100% isotopic purity. The succinic ²H₄ acid having high isotopic purity was also obtained on the hydrolysis of 1,2-ethanedinitrile with alkaline deuterium oxide. Based on the ¹H{²H} spectra analysis of N-(*o*-biphenyl)[2,3-²H₂]succinimide, it was elucidated that the Raney alloy reduction with alkaline deuterium oxide proceeds stepwise.

Key Words: Deuterium Labeling, Synthesis, Raney Alloy, NaOD-D₂O, Deuteriated Succinic Acid

INTRODUCTION

We have previously reported that halo-substituted aromatic compounds were reductively dehalogenated by employing Raney alloy in NaOD-D₂O to give the corresponding deuteriated forms in high isotopic purity.¹⁾⁻⁶⁾

Catalytic deuteration of maleic and fumaric acids and their esters with Pd/C provides an useful method for the incorporation of vicinal deuterium to succinic acid and its esters.⁷⁾⁻¹²⁾ This reductive method, however, requires deuterium gas not easy to handle as deuterium source. In addition, recently, we found that treatment of succinic [2,2,3,3-²H₄] anhydride with Pd/C in ethyl acetate afforded products in which more than expected numbers of deuterium atoms were introduced.¹³⁾

We herein report that Raney alloy reduction with 10% NaOD-D₂O was applied for reducing of fumaric acid and its dimethyl ester, and maleic anhydride, and acetylene dicarboxylic acid and its dimethyl ester, affording succinic [2,3-²H₂]- and [2,2,3,3-²H₄]-acids in high isotopic purity. It should be noted that hydrogen-deuterium exchange of deuteriated succinic acids obtained was not observed under the conditions used in this study. We also describe that succinic [2,2,3,3-²H₄]acid having high isotopic purity was prepared *via* the hydrolysis of 1,2-ethanedinitrile with alkaline deuterium oxide.

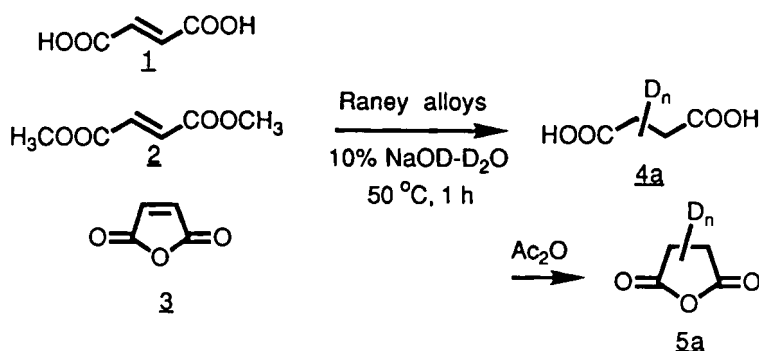
RESULTS AND DISCUSSION

Preparation of Succinic [2,3-²H₂]acid

The reductions of fumaric acid (1), dimethyl fumarate (2), and maleic anhydride (3) were carried out with Raney alloys such as Ni-Al and Cu-Al in 10% NaOD-D₂O. The results are summarized in Scheme 1 and Table 1. The isotopic purities of deuteriated succinic acids (4) prepared in this study were determined on the basis of the mass spectra of the corresponding deuteriated succinic anhydrides (5).

Fumaric acid (1) gave succinic [2,3-²H₂] acid (4a) only in 78% isotopic purity (Run 2), while dimethyl fumarate (2) and maleic anhydride (3), which have no proton source, were reduced with Cu-Al alloy, affording the desired acid (4a) in 95% and 100% isotopic purity (Runs 4 and 6).

However, the use of Ni-Al alloy caused the over-introduction of deuterium atoms due to hydrogen-deuterium exchange, so that 4a was obtained in a low isotopic purity (Runs 3, 5, and 7). It should be noted that the use of 350 mg of Cu-Al alloy in 10 ml of 10% NaOD-D₂O is necessary for giving 4a, because it was previously found that 300 mg of the alloy in 10 mL of 10% NaOH



Scheme 1

Table 1 Preparation of Succinic [²H₂]Acid (**4a**) and Succinic [²H₂] Anhydride (**5a**)^a.

Run	Substrate	Alloy	Yield (%) ^b		Composition of (5a) (%) ^c				
			4a	5a	D ₀	D ₁	D ₂	D ₃	D ₄
1 ^d	1	Cu-Al			no reaction				
2	1	Cu-Al	67	84	0	20	78	2	0
3	1	Ni-Al	61	57	0	53	36	10	1
4	2	Cu-Al	87	80	0	5	95	0	0
5	2	Ni-Al	85	67	0	14	52	17	17
6	3	Cu-Al	90	80	0	0	100	0	0
7	3	Ni-Al	83	70	0	20	49	18	13

a) Conditions; substrate, 5 mmol; 10% NaOD-D₂O, 10 mL; alloy, 350 mg. b) Isolated yields are shown. c) Determined by mass spectroscopic method. d) Amount of the alloy was 300 mg.

reduce 580 mg (5 mmol) of the acid (**1**).¹⁴

From the above results, the reductions of **1** were carried out in a mixture of 10% NaOH-H₂O and 10% NaOD-D₂O in order to investigate the relationship between deuterium content and volume ratios of D₂O and H₂O. The result is shown in Figure 1. Figure 1 shows that, in a mixture of 10% NaOD-D₂O and 10% NaOH-H₂O, it is more difficult for deuterium atoms to be introduced

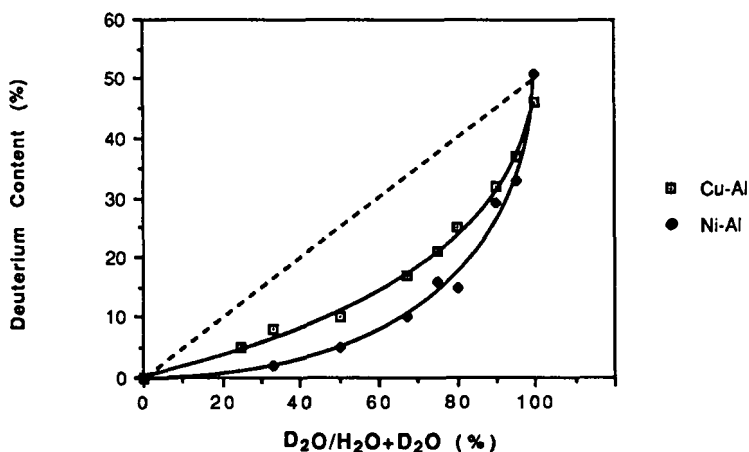


Figure 1 Variation of Deuterium Content of **4a** towards the Volume Ratios of 10% NaOD-D₂O and 10% NaOH-H₂O.

in **1** than hydrogen ones and the deuterium contents of **5** are lower than the expected values, especially in the case of Ni-Al alloy. This means that deuterium isotope effect appears during the above reduction, but the reason is not yet clear.

We previously reported that, in the reduction of 2-bromopentanoic acid using Cu-Al alloy, 2,3-dipropylsuccinic acid, which corresponds to an Ullmann coupling dimer, was formed as a by-product in 16% yield.¹⁴⁾ Based on this result, it is assumed that the reduction using Raney alloy proceeds stepwise. So, we investigated the reaction mechanism with Raney alloys in an alkaline deuterium oxide by using deuteriated acid (**4a**).

Succinic [$2,3\text{-}^2\text{H}_2$]acids prepared from **2** and **3** were converted to the corresponding *N*-(*o*-biphenyl)[$2,3\text{-}^2\text{H}_2$]succinimides (**6a**) and (**6b**),¹⁵⁾ and the aliphatic regions of their $^1\text{H}\{^2\text{H}\}$ spectra are shown in Figures 2 and 3.

When using 10% palladium-carbon as a catalyst, fumaric acid (**1**) and maleic acid (**7**) gave *meso*- and *d,l*-*N*-(*o*-biphenyl)[$2,3\text{-}^2\text{H}_2$]succinimides by the concerted addition of vicinal deuterium, and the methylene signals of the imides were appeared at 2.63 ppm and 2.85 ppm.¹⁵⁾ The signals of (**6a**) and (**6b**) were observed at 2.48 ppm and 2.68 ppm as a set of a singlet and a doublet with coupling constants of $J=4.5$ Hz indicating that the imides (**6a**) and

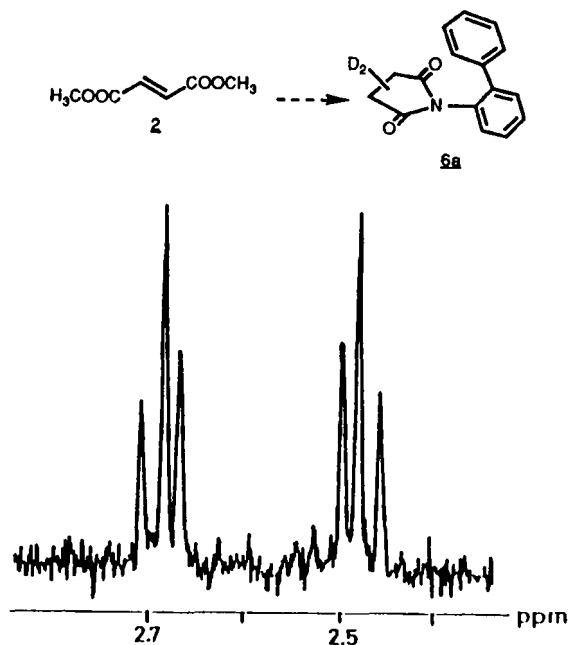


Figure 2 $^1\text{H}\{^2\text{H}\}$ of *N*-(*o*-biphenyl)[$2,3\text{-}^2\text{H}_2$]succinimides (**6a**).

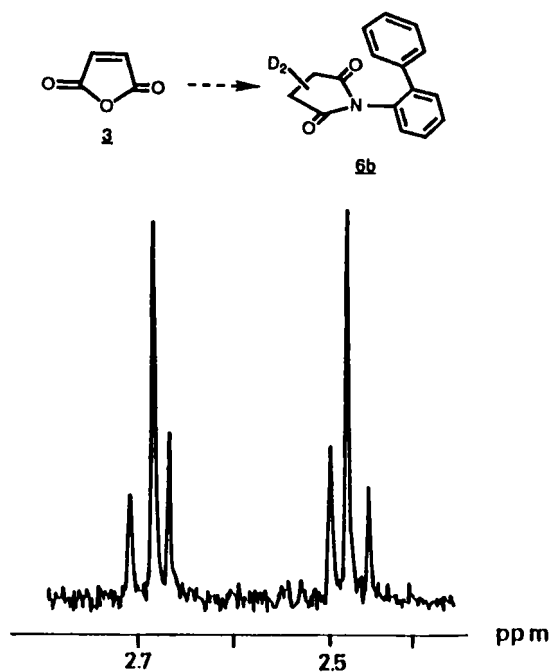
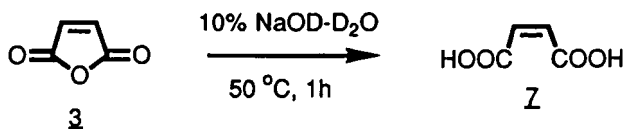


Figure 3 ¹H(²H) of N-(*o*-biphenyl)[2,3-²H₂]succinimides (**6b**).

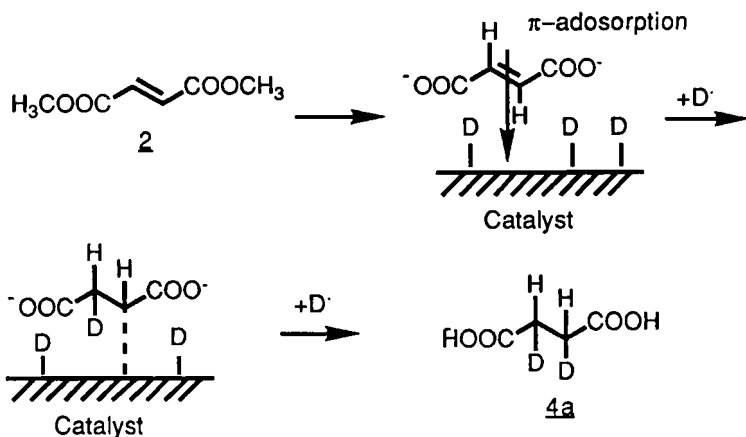
(**6b**) are 1:1 of *meso*- and *d,l*-forms.

Although it is well known that *cis* olefinic acid is isomerized to *trans* acid under the basic condition, the base-induced conversion from **3** to **1** did not occur; treating **3** in 10% NaOH at 50 °C for 1 h, maleic acid (**7**) was obtained in an almost quantitative yield (Scheme 2).



Scheme 2

From the the aboves, it is suggested that the reduction of **2** and **3** with Raney alloys in NaOD-D₂O proceeds stepwise, different from the case using palladium-carbon catalyst. The reaction mechanism is shown in Scheme 3.



Preparation of Succinic [2,2,3,3- $^2\text{H}_4$]Acid

The reductions of acetylene dicarboxylic acid (**8**), its dimethyl ester (**9**), and *meso*-2,3-dibromosuccinic acid (**10**) with Ni-Al and Cu-Al alloys in 10% NaOD-D₂O was carried out and the results are summarized (Scheme 4 and Table 2).

The reductions of **8** and **9** afforded the desired succinic[2,2,3,3- $^2\text{H}_4$]acid (**4b**) by using Ni-Al alloy in 60% yield and in 97% isotopic purity (Runs 2 and 3). Interestingly, the dibromo acid (**10**) gave, mainly, **4b** in 69% isotopic purity. When **10** was treated in 10% aqueous NaOH at 50 °C for 1 h, acetylenic acid (**8**) was formed in 70% yield. This suggests that the hydrobromination of **10** precedes the reductive debromination.

The [$^2\text{H}_4$]acid (**4b**) having high deuterium content could be obtained *via* the hydrolysis of 1,2-ethanedinitrile (**11**) in alkaline deuterium oxide such as 10% NaOD-D₂O, 20% Na₂CO₃-D₂O,

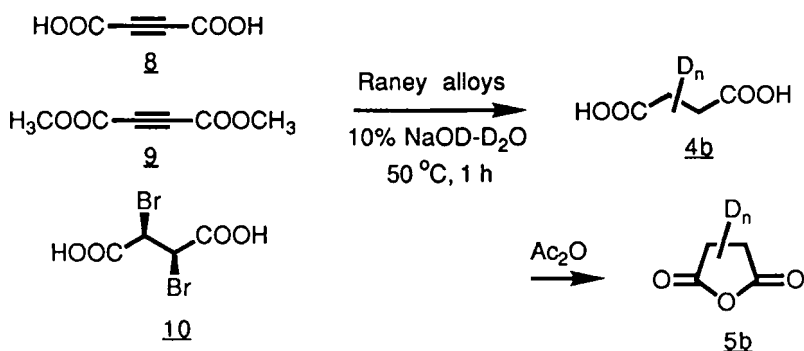


Table 2 Preparation of Succinic [²H₄]Acid (**4b**) and Succinic [²H₄] Anhydride (**5b**)^a.

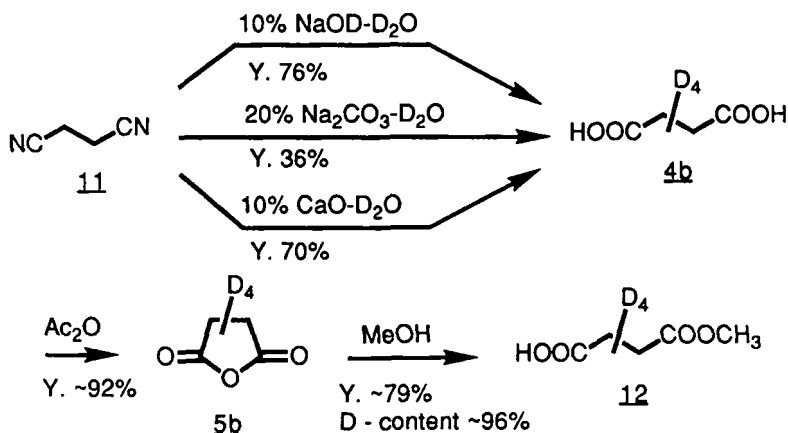
Run	Substrate	Alloy	Yield (%) ^b		Composition of (5b) (%) ^c				
			4b	5b	D ₀	D ₁	D ₂	D ₃	D ₄
1	8	Cu-Al	87	71	0	0	0	20	78
2	8	Ni-Al	60	75	0	0	0	3	97
3	9	Ni-Al	57	92	0	0	0	2	98
4	10	Cu-Al	67	84	0	0	13	42	45
5	10	Ni-Al	61	57	0	0	0	31	69

a) Conditions; substrate, 5 mmol; 10% NaOD-D₂O, 10 mL; alloy, 350 mg. b) Isolated yields are shown. c) Determined by mass spectroscopic method.

and 10% CaO-D₂O, as shown in Scheme 5.

The deuterium contents of the acid (**4b**) were determined on the basis of ¹H signal of methyl group of the corresponding deuterated methyl hydrogen succinate (**12**) as an internal reference. It should be noted that cheap Na₂CO₃ or CaO can be used as an alkaline media instead of expensive NaOD.

The deuterated positions of the acids (**4a**) and (**4b**) prepared in this study could be confirmed by their ¹³C{¹H} shown in Figure 4. The signals of deuterium-bounded carbon atoms were, as expected, observed as a triplet and quintet with coupling constants of *J*=19.7 Hz and *J*=20.2 Hz in higher field due to isotope effect



Scheme 5

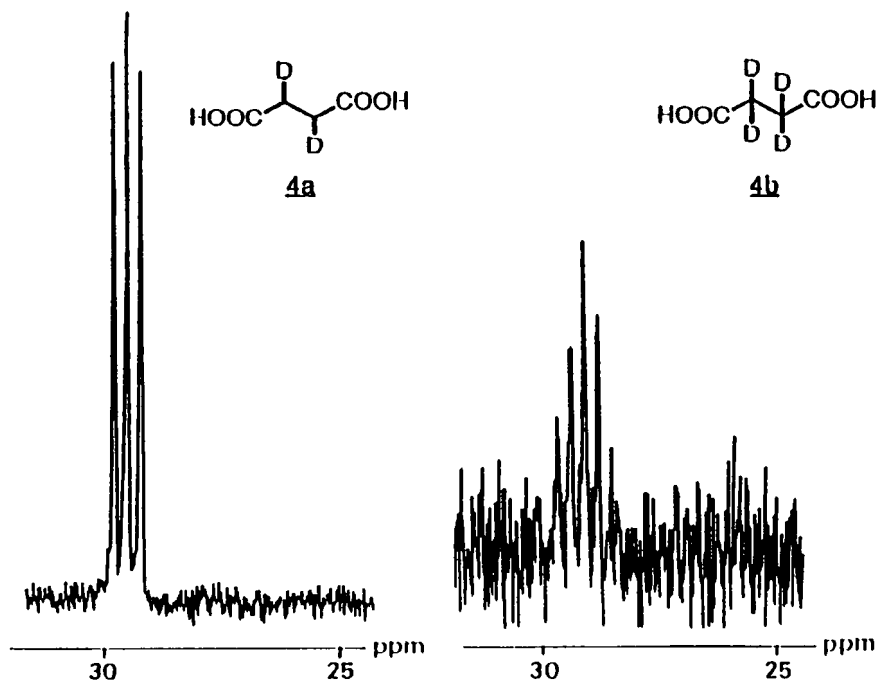


Figure 4 $^{13}\text{C}\{^1\text{H}\}$ of Deuteriated Succinic Acids (**4a-b**).

than those of hydrogen-bounded ones, respectively. This demonstrates that deuterium atoms are introduced at the desired positions of **4**.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-apparatus and are uncorrected. $^{13}\text{C}\{^1\text{H}\}$ were taken on a JEOL GSX-270 (67.94 MHz) n.m.r. spectrometer and $^1\text{H}\{^2\text{H}\}$ on a Hitachi R-90 H FT n.m.r. spectrometer in CD_3OD or CDCl_3 with Me_4Si as an internal reference. Mass spectra were recorded on a Nippon Denshi JMS-01SG-2 mass spectrometer at 75 eV using a direct inlet system.

Materials.

Compounds **1**, **2**, **3**, **8**, and **9** were commercially available. Compound **10** was prepared following the reported method.¹⁶⁾

Succinic [2,3- $^2\text{H}_2$]acid (**4a**).

To a vigorously stirred mixture of 490 mg (5 mmol) of maleic anhydride (**3**) and 10 mL of 10% $\text{NaOD-D}_2\text{O}$ was added 350 mg of Cu-Al alloy in small portions to maintain the temperature of the reaction mixture below 50 °C. After the reaction mixture had been

stirred at 50 °C for 1 h, it was cooled to room temperature. The above operation was carried out in a glove box under a nitrogen atmosphere. Then, the reaction apparatus was taken out from a box, and the formed Cu powder and unreacted alloy were filtered off using celite as a filter aid and washed with a small amount of water. The combined filtrates were acidified with concentrated hydrochloric acid to pH.1 under cooling and extracted with diethyl ether (50 mL X10 times). The extracts were dried over MgSO₄ and evaporated *in vacuo* to afford 525 mg (88%) of succinic acid [2,3-²H₂]acid (4a), m.p. 183-184 °C (lit., ¹⁷) 185 °C).

Succinic [2,2,3,3-²H₄]acid (4b).

Method A. (via the reduction with Raney alloy).

A mixture of 1.42 g (10 mmol) of dimethylacetylene dicarboxylate (7), 30 mL of 10% NaOD-D₂O, and 1.2 g of Ni-Al alloy was treated and worked up as above, giving 1.03 g (84%) of succinic [2,2,3,3-²H₄]acid (4b), m.p. 190-191 °C (lit., ¹⁷) 185 °C).

Method B. (via the hydrolysis of 1,2-ethanedinitrile (11)).

A mixture of 1.2 g (15 mmol) of 1,2-ethanedinitrile (11) in 20 mL of 10% NaOD-D₂O was heated under reflux for 1 h. After the reaction mixture was cooled to room temperature, it was acidified with concentrated hydrochloric acid to pH.1 under cooling and extracted with diethyl ether (60mL X10 times). The extracts were dried over MgSO₄ and evaporated *in vacuo* to yield 1.39 g (76%) of succinic [2,2,3,3-²H₄]acid (4b), m.p. 189-191 °C (lit., ¹⁷) 185 °C).

Succinic [2,3-²H₂]anhydride (5a).

After a stirred mixture of 446 mg (3.7 mmol) of succinic [2,3-²H₂]acid (4a) and 0.5 mL of acetic anhydride had been heated at 140 °C (bath temperature) for 20 min, it was cooled to room temperature. The precipitates which formed were filtered, washed with 10 mL of ether, and dried under a reduced pressure to afford 315 mg (83%) of succinic [2,3-²H₂]anhydride (5a) as colourless needles, m.p. 115-119 °C (lit., ¹⁸) 120 °C).

N-(*o*-biphenyl)[2,3-²H₂]succinimide (6a) and (6b).

Compounds (6a) and (6b) were prepared following the reported method, m.p. 134-136 °C (lit., ¹⁵) 134-135 °C).

Methyl hydrogen succinate[2,2,3,3-²H₄] (12).

After a mixture of 300 mg (2.9 mmol) of succinic [2,2,3,3-²H₄]anhydride (5b) in 235 mg of anhydrous MeOH had been heated under reflux for 20 min, it was evaporated *in vacuo* and the residue was recrystallized from CS₂ to afford 310 mg

(79%) of methyl hydrogen succinate[2,2,3,3- $^2\text{H}_4$] (12) as colourless plates, m.p. 49-52 °C (lit., ¹⁹) 58 °C).

REFERENCES

- 1) Tashiro, M., Iwasaki, A., and Fukata, G. - *J. Org. Chem.*, **43**: 136 (1978).
- 2) Tashiro, M., Nakayama, K., and Fukata, G. - *J. Chem. Soc., Perkin Trans. 1*, **1983**, 2315.
- 3) Tashiro, M., Mataka, S., Nakamura, H., and Nakayama, K. - *J. Chem. Soc., Perkin Trans. 1*, **1988**, 173.
- 4) Tashiro, M., Mataka, S., Nakayama, K., Tsuzuki H., and Yonemitsu, T. - *J. Chem. Res. (S)*, **1988**, 176.
- 5) Tashiro, M., Tsuzuki, H., Matsumoto, J.-I., Mataka, S., Nakayama, K., Tsuruta, Y., and Yonemitsu, T. - *J. Chem. Res.*, **1989**, (S) 372; (M) 2826.
- 6) Tashiro, M., Tsuzuki, H., Tsukinoki, T., Nakayama, K., Mataka, S., and Yonemitsu, T. - *J. Labeled Comp. Radiopharm.*, **28**, 703 (1990).
- 7) Tchen, T. T. and Milligan, H. V. - *J. Amer. Chem. Soc.*, **82**: 4115 (1960).
- 8) Childs, C. R. Jr. and Bloch, K. - *J. Org. Chem.*, **26**: 1630 (1960).
- 9) Osborn, J. A., Jardin, F. H., Young, J. F., and Wilkinson, G. - *J. Chem. Soc. A*, **1966**, 1711.
- 10) Chickos, J. S. - *J. Org. Chem.*, **44**: 780 (1979).
- 11) Chckos, J. S., Alul, R., and Baush, M. - *J. Org. Chem.*, **46**: 3559 (1981).
- 12) Chickos, J. S. - *J. Org. Chem.*, **51**: 553 (1986).
- 13) Tashiro, M., Tsuzuki, H., Yonemitsu, T. and Isobe, S., - The 52 nd Spring Annual Meeting of the Chemical Society of Japan, Abstract of Papers, **II**: 1372 (1987).
- 14) Tashiro, M., Mataka, S., Tsuzuki, H., Ogasahara, S., Isobe, S.-I., and Yonemitsu, T. - *Rep. Res. Inst. Ind. Sci. (Kyushu Daigaku Kinoh Busshitsu Kagaku Kenkyusho Hohkoku)*, **82**: 117 (1987).
- 15) Field, L. D., Kovac, C. A., and Stephenson, L. M. - *J. Org. Chem.*, **47**: 1358 (1982).
- 16) Rhinesmith, H. S. - *Org. Synth., Coll. Vol. 2*: 177 (1943).
- 17) Leffer, M. T. and Adams, R. - *J. Amer. Chem. Soc.*, **58**: 1551 (1936).
- 18) Jeffery, G. H. and Vogel, A. I. - *J. Chem. Soc.*, **1934**, 1103.
- 19) Bone, W. A., Sudborough, J. J., and Sprankling, C. H. G., - *J. Chem. Soc.*, **1904**, 539.