Pestic. Sci. 1996, **47**, 125–130

Studies of the New Herbicide KIH-6127. Part I. Novel Synthesis of Methyl 6-Acetylsalicylate as a Key Synthetic Intermediate for the Preparation of 6-Acetyl Pyrimidin-2-yl Salicylates and Analogues

Masatoshi Tamaru* & Yoshihiro Saito

K-I Chemical Research Institute Co., Ltd, Fukude-cho, Iwata-gun, Shizuoka 437-12, Japan

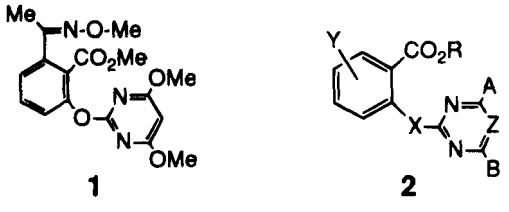
(Received 16 May 1995; revised version received 30 November 1995; accepted 3 January 1996)

Abstract: A novel synthesis of methyl 6-acetylsalicylate as a key synthetic intermediate for methyl 2-[(4,6-dimethoxypyrimidin-2-yl)oxy]-6-[1-(methoxyimino) ethyl]benzoate (KIH-6127) was studied, and directed at 6-substituted pyrimidin-2-yl salicylate herbicides and their analogues. Three synthetic approaches were successful: a modification of the Sandmeyer reaction of 6-acetylanthranilate (Method A), a direct ring-opening reaction of 3-methylphthalide using potassium permangamate and magnesium nitrate (Method B), and a regioselective ortholithiation of the protected 3-hydroxyacetophenone (Method C). These methods were applicable for the synthesis of various 6-acyl salicylates.

Key words: methyl 6-acetylsalicylate, herbicide, PS compound, KIH-6127, 6-acylsalicylate, 3-methylphthalide, ortholithiation.

1 INTRODUCTION

Methyl 2-[(4,6-dimethoxypyrimidin-2-yl)oxy]-6- [1-(methoxyimino)ethyl]benzoate (KIH-6127; Fig. 1, **1**)† has been found to be specifically effective against barnyard grass (*Echinochloa oryzoides* Frit.) over a wide range of growth stages including pre-emergence application, and has excellent crop safety in rice.[1,2] In this and two subsequent papers, we describe investigations into the synthesis of **1** and its analogues.



1 **2**

Fig. 1. Structures of compounds discussed in text: **1**, KIH-6127; **2**, pyrimidin-2-yl salicylate herbicides.

A series of pyrimidin-2-yl salicylates (Fig. 1, **2**) were previously reported[3] to have herbicidal activity. They act by inhibiting the plant enzyme acetolactate synthase (ALS), thereby blocking branched chain amino acid biosynthesis.[4]

The study of pyrimidin-2-yl salicylates bearing common functional groups has already been made. Although most such compounds have good herbicidal activity, few possess a broad spectrum of activity and acceptable crop safety suitable for commercial use.[5,6]

A study of 6-substituted pyrimidinyl salicylates was therefore undertaken in an attempt to find other candidates having these desired properties. For this, certain key synthetic intermediates containing a highly reactive functional group linked to the 6-position of the salicylate moiety was required to enable the preparation of a variety of 6-substitutions.

Previous studies of pyrimidin-2-yl salicylates have revealed the following: substitution at the 6-position of

* To whom correspondence should be addressed.

† The name pyriminobac-methyl has been proposed for this compound, but is not yet accepted by ISO.

Pestic. Sci. 0031-613X/96/$09.00

the salicylate moiety is preferable for herbicidal and ALS inhibitory activities; electron-withdrawing groups contribute to ALS activity; and hydrophilic groups lead to better activity against grass-weeds than broad-leaf weeds. We considered that a 6-acyl group could be of interest, since it would be both hydrophilic and have an electron-withdrawing effect. A 6-acyl compound could also be used as an intermediate for the conversion to corresponding ketals, alcohols and imino compounds.

We required a general and efficient synthetic method for the key intermediate methyl 6-acetylsalicylate (**3**). Such 6-acylsalicylates are virtually unknown, however, presumably because of the absence of a good synthetic route. In fact, only one process has been reported, in which methyl 6-acetylsalicylate, **3**, was obtained from 3-nitrophthalic anhydride, **4**, in poor yield.[7,8]

This report describes the development of novel synthetic routes for **3** which are more practical and efficient than the reported method. These synthetic schemes were investigated: (i) Method A: improvement of the literature procedure,[7,8] (ii) Method B: a direct ring-opening reaction of 7-methoxy-3-methylphthalide (**12**)[9,10] with potassium permanganate and magnesium nitrate, (iii) Method C: a directed *ortho*-lithiation of the protected 3-hydroxy acetophenone, **17**.[11–13]

2 MATERIALS AND METHODS

2.1 General procedure

[^{1}H]NMR spectra were recorded in δ (ppm) on a JEOL JMN-PMX-60Si in deuterochloroform, using trimethylsilane as an internal standard, while IR spectra and mass spectra were measured on Shimadzu IR-240 and JEOL JMS-SX-102A spectrometers, respectively. All melting points were uncorrected. The structures of compounds were confirmed by NMR, IR and mass spectroscopy.

Our three methods A, B and C are summarized in Figs 2–4. Other starting compounds were prepared by previously reported methods.[7–10]

Typical examples of synthetic procedures are given below.

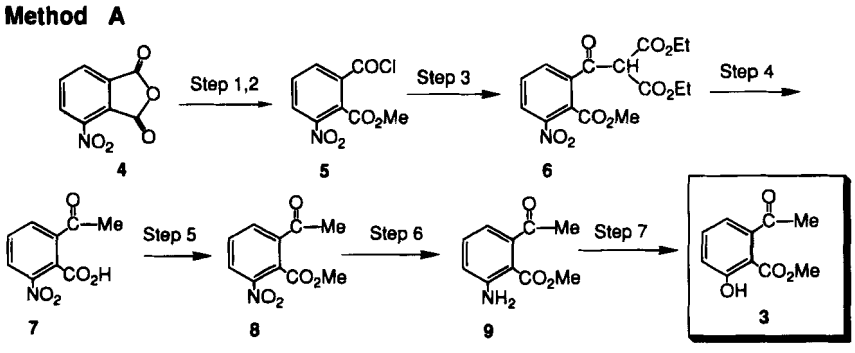
2.2 Syntheses of methyl 6-acetylsalicylate (3)

2.2.1 Method A (improvement in steps 3, 6, 7 of literature procedure; Fig. 2)

Crude acid chloride **5** was obtained by the reported methods.[7,8] Anhydrous magnesium chloride (100 g, 1·05 mol) was added to a mixture of diethylmalonate (160 g, 1 mol) in acetonitrile (500 ml) at 5°C for 10 min. Subsequently, triethylamine (210 g, 2·1 mol) was added at 0–5°C, and the mixture was stirred at room temperature for 1 h. After cooling to 0°C, a solution of crude **5** (234 g, 1 mol) in acetonitrile (50 ml) was added dropwise to the resulting mixture at 0–5°C, and the mixture stirred at room temperature for 2 h. The resulting solution was poured into a mixture of concentrated hydrochloric acid (20 ml) and ice/water (1·5 litre). The precipitate was collected by filtration, washed with water and dried to give crude **6** in 87% yield. This was then converted into **8** by the original method.[7]

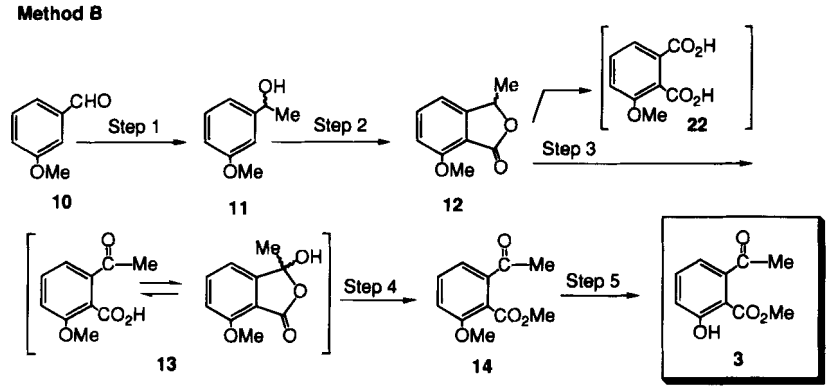
A solution of **8** (160 g, 0.7 mol) in ethyl acetate (500 ml) was subjected to hydrogenation in the presence of 10% Pd/C (12·5 g) under pressure (30 atm H_2) with cooling to below 30°C. The solution was filtered and the precipitate washed with ethyl acetate (50 ml × 3).

The combined ethyl acetate solutions were concentrated to give crude **9**, which was triturated with diisopropylether (IPE) + hexane (2 + 1 by volume; 250 ml) to give a light yellow powder, **9**, in 90% yield (124 g); m.p. 76–78°C (Lit.,[7] 76·5–77·5°C), [^{1}H]NMR δ: 2·46 (s, 3H), 3·83 (s, 3H), 5·17–5·66 (brs, 1H), 6·29–7·34 (m, 3H) ppm; IR (potassium bromide): 3500, 3450, 1710, 1690, 1280 cm^{-1}.



(Step 1) MeOH, reflux ; (Step 2) $SOCl_2$, reflux ; (Step 3) $MgCl_2$, Et_3N, $CH_2(CO_2Et)_2$, MeCN, 0-5°C then r.t ; (Step 4) conc. HCl, H_2O, 90°C ; (Step 5) MeI, K_2CO_3, MeCN, reflux ; (Step 6) H_2, Pd/C, AcOEt ; (Step 7) $NaNO_2$, conc. HCl, H_2SO_4, toluene, 83°C .

Fig. 2. Synthesis of methyl 6-acetylsalicylate (**3**) from 3-nitrophthalic anhydride (Method A).



(Step 1) MeMgI, ether-THF, r.t ; (Step 2) 2eq BuLi, hexane, CO_2 ; -60°C ;
(Step 3) $KMnO_4$, $Mg(NO_3)_2 \cdot 6H_2O$, H_2O, 70-80 °C, 3 hr ; (Step 4) MeI, K_2CO_3,
DMF, r.t , 20 hr ; (Step 5) 2.5 eq. BBr_3, CH_2Cl_2 , < -15°C .

Fig. 3. Synthesis of methyl 6-acetylsalicylate (**3**) from 3-methoxybenzaldehyde (Method B).

Sodium nitrite (15 g, 0·22 mol) was added to a solution of **9** (40 g, 0·21 mol) in a mixture of concentrated sulfuric acid (49 g), ice (200 g) and water (200 ml) held below 0°C, and the mixture stirred below 5°C for 10 min. This mixture was then added to a vigorously stirred mixture of toluene and water (2 + 1 by volume; 750 ml) at 83°C during 1 h. Stirring was continued for an additional 20 min. The resulting toluene layer was separated, washed with water, dried and concentrated to give crude crystals (28·5 g), which were washed with hexane + ethyl acetate (4 + 1 by volume; 28 ml) to give almost pure **3** in 65% yield (26 g); m.p. 95–96°C (Lit.,[7] 96–97°C), [^{1}H]NMR δ: 2·41 (s, 3H), 3·84 (s, 3H), 6·69–7·60 (m, 3H), 10·2 (s, 1H) ppm; IR (potassium bromide): 3200, 1700, 1590, 1470, 1370, 1300, 1280, 1190, 1120, 1070, 910, 760, 760 cm^{-1}; MS *m/z*: 194 (M^+).

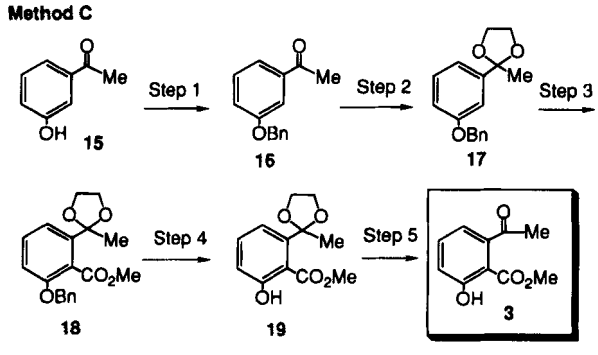
2.2.2 *Method B (direct ring opening reaction of a phthalide: Step 3; Fig. 3)*

Potassium permanganate (14·2 g, 0·09 mol) in water (200 ml) was added dropwise to a mixture of a solution of magnesium nitrate hexaphydrate (30·7 g, 0·12 mol) in water (250 ml) and **12**[9,10] (10·5 g, 0·059 mol) at 70–80°C over 3 h with vigorous stirring. The mixture was then stirred at 70–80°C for an additional hour.

The resulting precipitate (manganese dioxide) was filtered off and washed with diethyl ether (4 × 50 ml). The filtrate was extracted with ether (100 ml), washed with water, dried and concentrated to give crude **13** in 82% yield (8 g, 0·048 mol).

Without purification, **13** was treated with methyl iodide (7·2 g, 0·05 mol) in the presence of potassium carbonate (7 g, 0·05 mol) in *N*,*N*-dimethylformamide (50 ml) at room temperature for 20 h to give a crude residue **14** which was triturated with IPE + hexane (1 + 2 by volume; 30 ml) to afford pure **14** in 92% yield (7·95 g); m.p. 67–68°C (Lit.,[7] 65–65·5°C), [^{1}H]NMR δ: 2·25 (s, 3H), 3·78 (s, 3H), 3·86 (s, 3H), 6·86–7·66 (m, 3H) ppm; IR (potassium bromide): 3400, 3000, 1740, 1695, 1590, 1470, 1280, 1120, 1080 cm^{-1}.

A solution of **14** (7 g, 0·039 mol) in dichloromethane (50 ml) was treated with 2·5 equiv. boron tribromide (24 g, 0·098 mol) below −15°C for 2 h, then neutralized with aqueous sodium hydrogen carbonate. The dichloromethane layer was separated, dried and concentrated to give **3** in 35% yield (2·65 g); m.p. 95–96°C. The NMR and IR spectra were identical with those of the material produced by Method A.



(Step 1) BnBr, K_2CO_3, reflux, 5 hr ; (Step 2) $(EtO)_3CH$, $(HOCH_2)_2$,
p-TsOH, 120 °C, 1.5 hr ; (Step 3) BuLi, $ClCO_2Me$, toluene, r.t ;
(Step 4) H_2, Pd/C, AcOEt, r.t ; (Step 5) 5% HCl, MeOH, r.t, 6 hr.

Fig. 4. Synthesis of methyl 6-acetylsalicylate (**3**) from 3-hydroxyacetophenone (Method C).

2.2.3 *Method C (directed ortho-lithiation of protected 3-hydroxy acetophenone; Fig. 4)*

A mixture of 3-hydroxyacetophenone, **15** (34 g, 0·25 mol), benzyl bromide (47 g, 0·275 mol) and potassium carbonate (34·5 g, 0·25 mol) in acetonitrile (1 litre) was heated at reflux for 5 h. The precipitate was filtered off and washed with acetonitrile (3 × 60 ml). The combined acetonitrile solutions were concentrated to give crude **16**, which was distilled at b.p. 165–171°C/1·2 mm Hg to give 53·68 g of **16** as a colourless oil (95% yield); [^{1}H]NMR δ: 2·39 (s, 3H), 4·94 (s, 2H),

6·8–7·6 (m, 9H) ppm; IR (neat): 3000, 1680, 1480, 1580, 1435, 1350, 1270, 1020, 740, 680 cm^{-1}.

A mixture of **16**, triethoxymethane (227 g, 1·5 mol) and *para*-toluene sulfonic acid monohydrate (2·5 g) in ethylene glycol (375 ml) was stirred at 120°C for 1·5 h. The resulting mixture was extracted with toluene, washed with saturated sodium hydrogen carbonate and water, dried and concentrated to give **17** in 94% yield (64 g); m.p. 37–39°C; [^{1}H]NMR δ: 1·63 (s, 3H), 3·50–4·13 (m, 4H), 5·01 (s, 2H), 6·7–7·7 (m, 9H) ppm; IR (neat): 2960, 2860, 1590, 1480, 1440, 1375, 1260, 1200, 1030, 865, 700 cm^{-1}.

n-Butyllithium-hexane solution (1·6 M; 168 ml, 0·27 mol) was added to a solution of **17** (64 g, 0·23 mol) in toluene (500 ml) below 6°C during 30 min. The mixture was stirred at room temperature for 3 h, and cooled to 5°C. Methyl chloroformate (26 g, 0·27 mol) was added over 30 min to the resulting mixture, which was then stirred at room temperature for 2 h and poured into water. The organic layer was washed with water, dried and concentrated to give crude **18**, which was triturated with IPE + hexane (2 + 1 by volume; 250 ml) to give white crystals of **18** in 73% yield (55 g); m.p. 95–96°C; [^{1}H]NMR δ: 1·72 (s, 3H), 3·5–4·2 (m, 4H), 3·87 (s, 2H), 5·10 (s, 2H), 6·7–7·7 (m, 8H) ppm; IR (potassium bromide): 1720, 1580, 1450, 1260, 1030, 735 cm^{-1}; MS *m/z*: 328 (M^+).

A mixture of **18** (49 g, 0·15 mol) and 10% Pd/C (5 g) in ethyl acetate (500 ml) was stirred until the theoretical amount of hydrogen had been consumed. Filtration and concentration gave **19** in 95% yield (33·9 g); m.p. 142–143°C; [^{1}H]NMR δ: 1·83 (s, 3H), 3·4–4·2 (m, 4H), 3·92 (s, 2H), 6·7–7·5 (m, 3H) ppm; IR (potassium bromide): 3300, 1690, 1580, 1460, 1290, 1195, 1030, 800, 735 cm^{-1}.

A solution of **19** (29 g, 0·12 mol) in methanol (60 ml) was treated with 0·5% hydrochloric acid (4·2 g, 0·6 mmol) at 35°C for 4 h or 5% hydrochloric acid (1 g, 1·4 mmol) at room temperature for 6 h, neutralized with aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried and concentrated to afford **3** in 71% yield (16·5 g); m.p. 95–96°C.

Alternatively, a solution of **18** (39 g, 0·12 mol) in methanol (60 ml) was treated overnight with hydrogen in the presence of 10% Pd/C (3 g) and 5% hydrochloric acid (1 g, 1·4 mmol), giving **3** in 95% yield (22·1 g); m.p. 95–96°C. The NMR and IR spectra were identical with those of the material obtained by Method A.

3 RESULTS AND DISCUSSION

3.1 Method A (Fig. 2)

Our improvements in steps 3, 6 and 7 of Fig. 2 have the following advantages over the conventional methods.[7,8]

Instead of using a large excess of ethyl malonate and magnesium methoxide, we have found that a combination of one molar equivalent of ethyl malonate and magnesium chloride, and two molar equivalents of triethylamine[14] gave **6** in excellent yield (87%). As a result, the work-up procedure was much simpler since the need to remove a large excess of ethyl malonate was eliminated.[7]

Hydrogenation of **8** under pressure (30 atm H_2) was found to reduce the reaction time (from 8 h to 1 h) in step 6. The yield of **9** was strongly dependent on the solvent employed. Hydrogenation performed in ethyl acetate gave **9** in excellent yield (90%). The use of methanol gave two by-products **20** and **21** as shown in Fig. 5, together with a moderate yield of **9** (*c.* 70%).

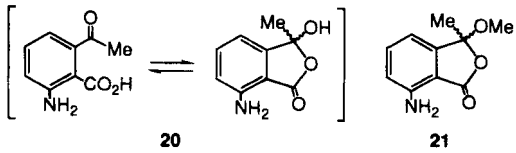
In the final step, hydroxylation of the diazonium salt of **9** gave a low yield of **3** (32%) as reported[8] with poor reproducibility. Use of a two-phase system (toluene/10% hydrochloric acid) in the Sandmeyer reaction of **9** was explored to give **3** in an improved yield since further degradation of the product **3** was prevented.

3.2 Method B (Fig. 3)

Because of the low overall yield in the seven-stage synthesis of Method A, we examined other approaches to **3**. For the construction of **3**, a direct ring-opening reaction of protected 7-hydroxy-3-methylphthalide was considered to be an important step as shown in Fig. 3. 7-Methoxy-3-methylphthalide **12** was readily prepared from commercially available 3-methoxybenzaldehyde **10** (steps 1, 2).[9,10]

After unsuccessful attempts using conventional methods such as Jones reagent in acetone, we assumed that the ring-opening reaction under acidic conditions may precede further oxidation, and re-cyclization to the γ-lactone.

The ring-opening reaction of **12** with aqueous potassium permanganate under alkaline conditions afforded only undesired 3-methoxyphthalic acid **22** in 61% yield, which is presumably formed by further oxidation of **13**. In the oxidation of 1,2-bis(1-hydroxyethyl) benzene with potassium permanganate, the addition of magnesium nitrate hexahydrate has been reported to be effective for preventing over-oxidation to form 1,2-diacetylbenzene magnesium salt.[15] Application of this reaction mixture to our ring-opening reaction of **12**, followed by methylation, resulted in clean conversion to **14** in good overall yield (75%).



20 21

Fig. 5. Two major by-products in hydrogenation of **8**.

In the final step, a selective demethylation of the 2-methoxy group of **14** was performed with 2·5 equiv. boron tribromide below −15°C to give **3**.

3.3 Method C (Fig. 4)

Although the above Methods A and B are satisfactory for most purposes for the syntheses of a variety of 6-sustituted pyrimidin-2-yl salicylates, we required a more economic procedure for the key intermediate **3** in the KIH-6127 project under study. According to other reports,[16,17] directed *ortho*-lithiation of a protected 1,3-disubstituted compound such as **17** should be feasible, which, after methoxycarbonylation, should afford **18** as depicted in Fig. 4.

This synthetic approach commenced with protection of the hydroxy group of **15**. Thus, benzylation of **15** with 1·1 equiv. of benzyl bromide in the presence of potassium carbonate in acetonitrile gave **16** in 90% yield.

Next, the acetyl group of **16** was protected using an excess of ethylene glycol in the presence of *para*-toluenesulfonic acid in refluxing toluene for 8 h, to give **17** in 74% yield. Even after this prolonged reaction, some starting materials **16** still remained. When the mixture of **16** and ethylene glycol was treated at 120°C for 1·5 h in the presence of triethoxymethane (6 equiv.) in order to transacetalize, a dramatic rate enhancement (from 16 h to 1·5 h) was observed. Analysis of the organic layer (GLC) revealed a 94% yield of **17**.

The directed *ortho*-lithiation of **17** was then examined. As cryogenic reactions are undesirable from an industrial point of view, the reaction was tried around room temperature. The intermediate lithium salt proved to be stable enough to proceed following methoxycarbonylation at room temperature, which is a great advantage.

Treatment of **17** with phenyl lithium or butyl lithium in various solvents, followed by addition of methyl chloroformate, gave **18** in 13–73% yields as shown in Table 1.

The yields of lithiation followed by methoxycarbonylation were found to be dependent upon the solvent employed. It was fortunate that toluene, which is a preferred solvent for industrial use, gave excellent results. In order to examine the relationship between solvent type and the yield of **18**, the lithiation reaction in twice the normal volume of hexane (a half molar concentration of lithium) was examined. The generated lithium salt of **17** was clearly soluble and resulted in a much higher yield of **18** (55–66%). This finding suggests that the reaction depends on the solubility of the lithium salt of **17**.

Subsequent deprotections, i.e. reduction of the benzyl group and hydrolysis of the ketal, of **18** and **19**, gave **19** and **3** in 95 and 71% yields, respectively. Alternatively, simultaneous deprotection of the benzyl and ketal groups could be performed to give **3** in 95% yield, with hydrogenation on Pd/C in the presence of a catalytic amount of hydrochloric acid.

TABLE 1
Lithiation & Methoxycarbonylation of **17** in Various Solvents[a]

Reagents	*Solvents*[b]	*Yield* (%)[c]
PhLi	Hexane	13
(15% benzene sol.)	Ether	14
	Benzene	54
BuLi	Hexane	22
(15% hexane sol.)	Benzene	53
	Toluene	73
	Hexane[d]	55–66

[a] **17**: Li reagent: $ClCO_2Me$ = 1 : 1·17 : 1·1 (equiv.).
[b] 0·38 M concentration.
[c] Isolated yield.
[d] Twice vol. of hexane (0·19 M) was used.

This efficient procedure gave **3** in high overall yield (65%) based on starting **15**, with Method C being clearly superior to Methods A and B. A variety of 6-acylsalicylates could also be obtained by employing Method C. Method C holds a key position as a novel synthetic route for the preparation of **1**.

In conclusion, we have succeeded in developing a novel synthetic route to **3**.

ACKNOWLEDGEMENTS

We wish to express our thanks to Prof. Toshio Fujita, Kyoto University, for his invaluable suggestions. We also thank Dr Yoshikazu Kimura, Ihara Chemical Industry Co., Ltd, for fruitful discussions.

REFERENCES

1. Tamaru, M., Kawamura, N., Sato, F., Tachikawa, S., Yoshida, R. & Takabe, F., Kumiai Chemical Ind., Co., Ltd & Ihara Chemical Ind., Co., Ltd, Eur. Pat. Appl., EP-435170, 1991.
2. Hanai, R., Kawano, K., Shigematsu, S. & Tamaru, M., *Proc. Brighton Crop Prot. Conf.—Weeds*, **1** (1993) 47–52.
3. Shimizu, T., Nakayama, I., Nakao, T., Nezu, Y. & Abe, H., *Nihon Noyaku Gakkaishi* (*J. Pestic. Sci.*), **19** (1994) 59–67.
4. Ray, T. B., *Plant Physiol.*, **75** (1984) 827–31.
5. Takahashi, S., Shigematsu, S., Morita, A., Nezu, Y., Clans, J. S. & Williams, C. S., *Proc. Brighton Crop Prot. Conf.—Weeds*, **1** (1991) 57–62.
6. Wada, S., Saito, Y., Kaku, K., Nezu, M. & Shigematsu, S., *Annual Meeting of Pesticide Society of Japan* (1992) 15 (in Japanese).
7. Horii, Z., Tamura, Y., Okumura, K. & Kugita, H., *Yakugaku Zasshi*, **74** (1954) 466–470; *Chem. Abstr.*, **49** (1955) 6882*c*.
8. Baker, B. R., Schaub, R. E., Josephan, J. P., McEvoy, F. J. & Williams, J. H., *J. Org. Chem.*, **17** (1952) 164–8.

9. Buehler, C. A., Powers, T. A. & Michels, J. G., *J. Am. Chem. Soc.*, **66** (1944) 417–18.
10. Uemura, M., Tokuyama, S. & Sakan, T., *Chem. Lett.*, (1975) 1195–8.
11. Tamaru, M., Kawamura, N., Sato, M., Takabe, F., Tachikawa, S. & Yoshida, R., Kumiai Chemical Ind., Co., Ltd & Ihara Chemical Ind., Co., Ltd, Jpn Kokai Tokkyo Koho, JP 4-134080 (1993).
12. Umezu, K., Isozumi, K., Miyazaki, T., Tamaru, M., Takabe, F., Masuyama, N. & Kimura, Y., *SYNLETT* (1) (1994) 61–2.
13. Tamaru, M., Umezu, K., Isozumi, K., Maejima, C., Kageyama, H. & Kimura, Y., *Synth. Commun.*, **24** (1994) 2749–56.
14. Rathke, M. W. & Cowan, R. J., *J. Org. Chem.*, **50** (1985) 2622–4.
15. Goldschmidt, S. & Zoebelein, A., *Chem. Ber.*, **94** (1961) 169–73.
16. Snieckus, V., *Chem. Rev.*, **90** (1990) 879–979.
17. Uemura, M., Nishikawa, N., Take, K., Ohnishi, M., Hirotsu, K., Higuchi, T. & Hayashi, Y., *J. Org. Chem.*, **48** (1983) 2349–60.