EFFICIENT OLEFIN SYNTHESIS USING THE PYRAZINYLSULFINYL GROUP

Akihiro Ohta*, Yoshiko Tonomura, Hiroko Odashima,
Nahoko Fujiwara, and Makoto Shimazaki
Tokyo College of Pharmacy
1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

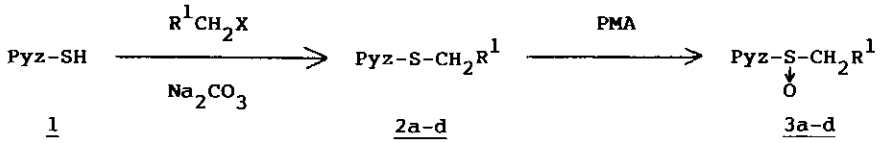
Abstract —— Ethyl cinnamates, stilbenes and 1,4-diaryl-1,3-butadienes were prepared using the pyrazinylsulfinyl group as a leaving group to affect ß-elimination.

The heating of sulfoxides induces ß-elimination of the sulfinyl group to give the corresponding olefins.[1] This reaction often serves as a method for the synthesis of naturally occurring compounds with unsaturated bonds.[2] The pyrazinylsulfinyl group, used as a leaving group to form a double bond in the reaction, was found to serve as a good leaving group, and efficiently promoted the synthesis of cinnamonitriles from chloroacetonitrile and benzyl bromides.[3] This group was thus used for the preparation of other olefins, following the procedure for the synthesis of cinnamonitriles. In this paper, the synthesis of ethyl cinnamates, stilbenes and butadienes is described.

Coupling reactions of 3,6-diisopropyl-2-pyrazinethiol (**1**)[4] with alkyl halides (R^1CH_2X) proceeded by stirring the mixture of Na_2CO_3 and the two materials in acetone at room temperature and the results are shown in Table 1. All the products (**2a-d**) were oxidized with permaleic acid (PMA), prepared from 90% H_2O_2 and maleic anhydride, to give the corresponding sulfoxides (**3a-d**).

Based on previous results[3], it was considered that treatment of these sulfoxides (**3a-d**) with a suitable base followed by reactions with alkyl halides (R^2CH_2X) would give pyrazinylsulfinyl compounds (**4**), whose likely instability would render themselves easily pyrolysable to the corresponding olefins ($R^1CH=CHR^2$). This was actually found to be the case, as shown in Scheme 1.

Table 1. Synthesis of Alkylsulfinylpyrazines (3a-d)

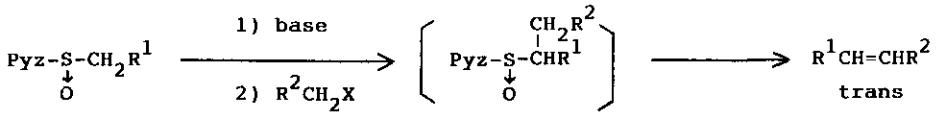


1 2a-d 3a-d

R^1	X	Products (Yields %)	
EtOCO	Cl	2a (99)	3a (91)
Ph	Br	2b (75)	3b (94)
3,5-$(MeO)_2Ph$[5]	Br	2c (94)	3c (94)
3,4,5-$(MeO)_3Ph$[6]	Br	2d (95)	3d (97)

Pyz = 3,6-Diisopropyl-2-pyrazinyl, PMA = Permaleic Acid

Scheme 1

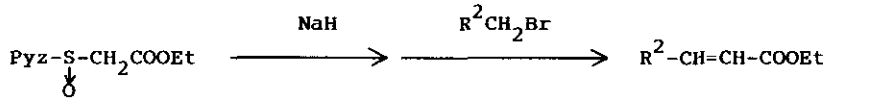


3a-d 4 5-7

Pyz = 3,6-Diisopropyl-2-pyrazinyl

First, ethyl cinnamates (5a-d) were prepared by reactions of 3,6-diisopropyl-2-ethoxycarbonylmethylsulfinylpyrazine (3a) with benzyl bromides under the same conditions as used for the synthesis of cinnamonitriles[3]. However, the target cinnamates were obtained within a limitation of 60% yields and in all cases, their configuration was trans. To obtain better yields, potassium diisopropylamide (KDA) was used as the base but this led to the formation of many by-products, which were inseparable from ethyl cinnamates even by low pressure chromatography.

Table 2. Synthesis of Ethyl Cinnamates (5a-d)

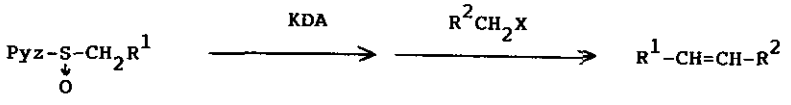


3a 5a-d

R^2	Products (Yields %)	Mp (°C) or Bp (°C/torr)
Ph	5a (37)	90-100*/4 [271/760][7]
p-MePh	5b (39)	110-115*/3 [163-165/25][8]
p-NO_2Ph	5c (31)	134-135 [136][9]
p-BrPh	5d (60)	110-120*/3 [180-183/30][8]

Pyz = 3,6-Diisopropyl-2-pyrazinyl, * Oil bath temperature

Table 3. Synthesis of Stilbenes (6a-k)

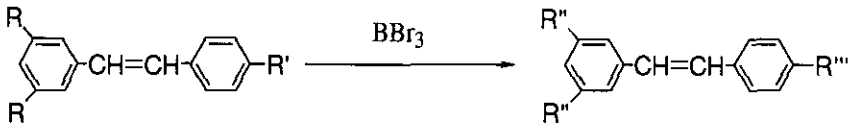


3b-d 6a-k

Sulfoxides	R^2	X	Products (Yields %)	Mp (°C)
3b	Ph	Br	6a (95)	114-118 [124][10]
	o-MePh	Br	6b (56)	30-32 [31-32][11]
	m-MePh	Br	6c (90)	48-49 [51.5-52.5][12]
	p-MePh	Br	6d (94)	111-115 [120][13]
	p-BrPh	Br	6e (90)	128-131 [138][12]
	p-NO_2Ph	Br	6f (35)	154-155 [155][14]
	p-MeOPh	Cl	6g (65)	133-135 [136][12]
3c	Ph	Br	6h (92)	54-55 [55-56][16]
	p-MeOPh	Cl	6i (69)	51-53 [---]*
	p-BzOPh	Br	6j (54)	105-106
3d	3,4,5-$(MeO)_3$Ph	Br	6k (73)	222-224 [211-212][6]

Pyz = 3,6-Diisopropyl-2-pyrazinyl, KDA = Potassium Diisopropylamide
* This mp is not presented in any literatures but the ^{1}H-nmr data agreed with reported one[17].

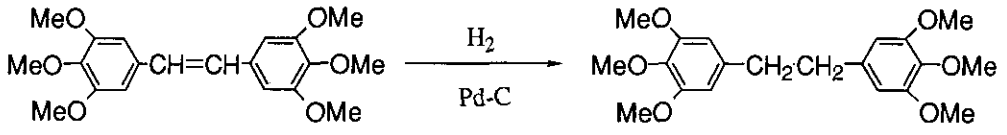
Scheme 2



6g-i

Stilbenes	Products
6g (R=H, R'=OMe)	4-Hydroxystilbene[17] (R"=H, R"'=OH)
6h (R=OMe, R'=H)	Pinosylvin[17] (R"=OH, R"'=H)
6i (R=OMe, R'=OMe)	Resveratrol[19] (R"=OH, R"'=OH)

Scheme 3

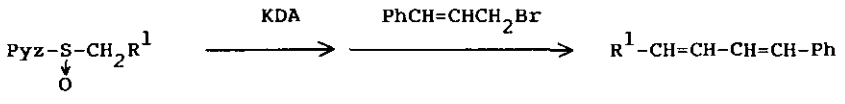


6k Brittonin A[6]

The synthesis of stilbenes (**6a-k**) *from 3,6-diisopropyl-2-benzylsulfinylpyrazines* (**3b-d**) and benzyl bromides was subsequently conducted using sodium hydride as the base but sufficient yields were not given. However, in contrast to the synthesis of ethyl cinnamates, KDA provided much better yields, as evident from Table 3. All stilbenes thus obtained had the trans form. Many naturally occurring stilbenes are known and possess antifungal action.[15] In recent years, it becomes of interest that 3,5,4'-trihydroxystilbene (resveratrol) inhibits the deposition of triglyceride and cholesterol in the liver of rats fed corn oil-cholesterol-cholic acid mixture.[16] Luk et al. prepared 3,5-dihydroxystilbene (pinosylvin), which was isolated from the heart wood of Indian Pinus excelsa,[5] by demethylation of 3,5-dimethoxystilbene (**6h**) with boron tribromide.[17] By this demethylation of **6g** and **6i**, we obtained 4-hydroxystilbene and resveratrol in 99% and 88% yields, respectively (Scheme 2). Some synthetic procedures for these stilbenes are known[18] but the way to prepare them from two kinds of benzyl halides is presented for the first time. An allergy-inducing component, brittonin A, isolated from the ground material of Frullania brittoniae subsp. truncatifolia, is obtained by catalytic hydrogenation of 3,4,5,3',4',5'-hexamethoxystilbene (**6k**) as shown in Scheme 3.[6]

Next, 1,4-diaryl-1,3-butadienes (**7a-c**) were prepared from benzyl bromides and cinnamyl bromides, under the same conditions as those for the preparation of stilbenes. The results are shown in Table 4. From the ^{1}H-nmr spectral data of **7a-c**, it is considered that the configuration based on the two double bonds of the butadiene part is 1-(E)-3-(E) form.

Table 4. Synthesis of 1,4-Diphenyl-1,3-butadienes (7a-c)



3b-d **7a-c**

Sulfoxides	Products (Yields %)	Mp (°C)
3b	7a (98)	151-151 [149-150][21]
3c	7b (59)	64-65
3d	7c (49)	87-88

Pyz = 3,6-Diisopropyl-2-pyrazinyl, KDA = Potassium Diisopropylamide

Use of the pyrazinylsulfinyl group as the leaving group should easily lead, as shown below, to the efficient production of various olefins, using two alkyl halides.

1. The reaction proceeds within a short time under relatively mild conditions, unlike the case of using phenylsulfinyl group whose elimination is time consuming.
2. Pyrazinylsulfinyl compounds are easily prepared from pyrazinethiols which do not have the offensive odor characteristic of mercaptans.

EXPERIMENTAL

None of the melting or boiling points are corrected. ^{1}H-Nmr spectral data of new compounds were given by Varian EM-390 using TMS as an internal standard and the configuration of olefins prepared was determined on the basis of the ^{1}H-nmr spectra given by Brucker AM-400. The following instruments were used to obtain other spectral data. Ir spectra: Japan Spectroscopic Co. A-100; Ms: Hitachi M-80B spectrometer.

General Procedure for the Preparation of 2-Alkylthio-3,6-diisopropylpyrazines (2a-d)

The mixture of alkyl halides (10.2 mmol), 3,6-diisopropyl-2-pyrazinethiol (1.13 g, 10 mmol), Na_2CO_3 (1.69 g, 16 mmol) and Me_2CO (90 ml) was stirred for 15 h at room temperature and worked up according to the previous report[3].

2-(3,5Dimethoxybenzylthio)-3,6-diisopropylpyrazine (**2c**) was obtained as a crude product including by-products which could not be removed off, so that its spectroscopic and analytical data are not presented.

2-Ethoxycarbonylmethylthio-3,6-diisopropylpyrazine (2a)

Colorless viscous oil; bp 92-95°C/0.05 torr; yield: 99%; ms: m/z 282 (M^+), 195 (M^+-CH_2COOEt); ir (neat): 1760 (ν_{CO}) cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.15 (t, J = 7 Hz, 3H, $COOCH_2\underline{CH_3}$), 1.16 (d, J = 7 Hz, 6H, $CH(\underline{CH_3})_2$), 1.18 (d, J = 7 Hz, 6H, $CH(\underline{CH_3})_2$), 2.81-3.36 (m, 2H, 2 X $\underline{CH}(CH_3)_2$), 3.92 (s, 2H, $S\underline{CH_2}COOEt$), 4.19 (q, J = 7 Hz, 2H, $COO\underline{CH_2}CH_3$), 8.07 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{14}H_{22}N_2O_2S$: C, 59.54; H, 7.85; N, 9.92. Found: C, 59.81; H, 7.96; N, 10.19.

2-(3,4,5-Trimethoxybenzylthio)-3,6-diisopropylpyrazine (2d)

Colorless needles; mp 50-51°C (n-hexane); yield: 96%; ms: m/z 376 (M^+); ^{1}H-nmr ($CDCl_3$): δ 1.24 (d, J = 5 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.32 (d, J = 5 Hz, 6H, $CH(C\underline{H}_3)_2$), 2.88-3.33 (m, 2H, 2 X $C\underline{H}(CH_3)_2$), 3.77 (s, 9H, 3 X OCH_3), 4.34 (s, 2H, SCH_2Ph), 6.59 (s, 2H, benzene H), 8.01 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{20}H_{28}N_2O_3S$: C, 63.80; H, 7.50; N, 7.44. Found: C, 63.83; H, 7.52; N, 7.38.

General Procedure for Preparation of 2-Alkylsulfinyl-3,6-diisopropylpyrazines (3a-d)

The preparation of 2-benzylsulfinyl-3,6-diisopropylpyrazine (**3b**) from **2b** was previously presented[21] and the other 2-alkylsulfinyl-3,6-diisopropylpyrazines (**3a,c,d**) were prepared from **2a,c,d** according to the reported method[3]. (**2c** was used for the synthesis of **3c** without purification and the yield of **3c** was calcurated from **1c**.)

2-Ethoxycarbonylmethylsulfinyl-3,6-diisopropylpyrazine (3a)

Colorless viscous oil; bp 79-90°C/0.06 torr; yield: 91%; ms: m/z 298 (M^+), 211 (M^+-CH_2COOEt); ir (neat): 1030 (ν_{SO}), 1740 (ν_{CO}) cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.08 (t, J = 7.3 Hz, 3H, $COOCH_2C\underline{H}_3$), 1.25 (d, J = 6.6 Hz, 3H, $CH(C\underline{H}_3)CH_3$), 1.26 (d, J = 6.9 Hz, 3H, $CH(C\underline{H}_3)CH_3$), 1.28 (d, J = 6.9 Hz, 3H, $CH(C\underline{H}_3)CH_3$), 1.29 (d, J = 6.6 Hz, 3H, $CH(C\underline{H}_3)CH_3$), 3.02-3.50 (m, 1H, $C\underline{H}(CH_3)_2$), 3.57-3.95 (m, 1H, $C\underline{H}(CH_3)_2$), 4.06 (q, J = 7 Hz, 2H, $COOC\underline{H}_2CH_3$), 4.14 (d, J = 15 Hz, 1H, $SOCH_aCOOEt$), 4.52 (d, J = 15 Hz, 1H, $SOCH_bCOOEt$), 8.60 (s, 1H, pyrazine H); High resolution ms Calcd for $C_{14}H_{22}N_2O_3S$: 298.1353. Found: 298.1342.

2-(3,5-Dimethoxybenzylsulfinyl)-3,6-diisopropylpyrazine (3c)

Colorless needles; mp 94-96°C (n-hexane); yield: 95%; ms: m/z 362 (M^+); ir (KBr): 1060 (ν_{SO}) cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 0.89 (d, J = 7 Hz, 3H, $CH(C\underline{H}_3)CH_3$), 1.21 (d, J = 7 Hz, 3H, $CH(C\underline{H}_3)CH_3$), 1.42 (d, J = 7 Hz, 6H, $CH(C\underline{H}_3)_2$), 3.13-3.48 (m, 2H, 2 X $C\underline{H}(CH_3)_2$), 3.66 (s, 6H, 2 X OCH_3), 4.34 (d, J = 12 Hz, 1H, SCH_aPh), 4.51 (d, J = 12 Hz, 1H, SCH_bPh), 6.12 (d, J = 3 Hz, 2H, benzene H), 6.33 (t, J = 3 Hz, 1H, benzene H), 8.53 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{17}H_{22}N_2OS$: C, 67.51; H, 7.33; N, 9.26. Found: C, 67.48; H, 7.44; N, 9.38.

2-(3,4,5-Trimethoxybenzylsulfinyl)-3,6-diisopropylpyrazine (3d)

Colorless needles; mp 134-136°C (Et_2O); yield: 97%; ms: m/z 392 (M^+); ir (KBr): 1040 (ν_{SO}) cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 0.89 (d, J = 7.2 Hz, 3H, $CH(C\underline{H}_3)CH_3$), 1.19 (d, J = 6.6 Hz, 3H, $CH(C\underline{H}_3)CH_3$), 1.40 (d, J = 6.3 Hz, 6H, $CH(C\underline{H}_3)_2$), 3.08-3.56 (m, 2H, 2 X $C\underline{H}(CH_3)_2$), 3.68 (s, 6H, 2 X OCH_3), 3.72 (s, 3H, OCH_3), 4.29 (d, J = 12 Hz, 1H, SCH_aPh), 4.44 (d, J = 12 Hz, 1H, SCH_bPh), 6.17 (s, 2H, benzene H), 8.52 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{20}H_{28}N_2O_4S$: C, 61.20; H, 7.19; N, 7.14. Found: C, 61.09; H, 7.32; N, 6.92.

General Procedure for the Preparation of Ethyl Cinnamates (5a-d) by Reaction of 3a and Benzyl Bromides

To the yellow solution prepared by stirring a mixture of **3a** (596 mg, 2 mmol), 60% NaH (96 mg, 2.4 mmol) and 1,2-dimethoxyethane (30 ml) at room temperature for 10 min was added the suitable benzyl bromide (2.4 mmol). The solution was refluxed for 1 h and worked up according to the procedure for the syntheses of cinnamonitriles[3].

General Procedure for the Preparation of Stilbenes (6a-k) by Reaction of 3b-d and Benzyl Halides

To the solution of potassium diisopropylamide (KDA) in THF (15 ml) prepared from LDA (2.4 mmol) and tert-BuOK (2.4 mmol) was added successively the sulfoxides **3b-d** (2 mmol) and a suitable benzyl halide (2.4 mmol) at -78°C, and the mixture was stirred at room temperature for 1 h, then refluxed for 1 h. After removal of the solvent by distillation in vacuo, the residue was extracted with Et_2O and the organic layer was washed with 5% HCl, dried over Na_2CO_3 and evaporated. The residue was purified by low pressure liquid chromatography (Kieselgel 60, 230-400 mesh, Hexane-Et_2O) to give stilbenes (**6a-k**).

(E)-4'-Benzyloxy-3,5-dimetoxystilbene (6j)

Colorless needles; mp 105-106°C (n-hexane); yield: 54%; ms: m/z 346 (M^+), 255 (M^+-CH_2Ph); ^{1}H-nmr ($CDCl_3$): δ 3.84 (s, 6H, 2 X OCH_3), 5.10 (s, 2H, OCH_2Ph), 6.39 (t, J = 2 Hz, 1H, 4-H-Ph), 6.66 (d, J = 2 Hz, 2H, 2,5-H_2-Ph), 6.91 (d, J = 16 Hz, 1H, $C\underline{H}_a$=CH_b), 6.98 (d, J = 9 Hz, 2H, 3',4'-H_2-Ph), 7.05 (d, J = 16 Hz, CH_a=$C\underline{H}_b$), 7.45 (d, J = 9 Hz, 2H, 2',6'-H_2-Ph), 7.32-7.47 (m, 5H, $\underline{H}_5$-$PhCH_2O$) ppm; Anal. Calcd for $C_{23}H_{22}O_3$: C, 79.74; H, 6.40. Found: C, 79.74; H, 6.01.

General Procedure for the Preparation of 1,4-Diaryl-1,3-butadienes (7a-c) by Reaction of 3b,c,d and Cinnamyl Bromides

The preparation of 1,4-diaryl-1,3-butadienes (**7a-c**) was accomplished by the reaction of **3b,c,d** and a cinnamyl bromide according to the method for the syntheses of **6a-k**.

1-(3,5-Dimethoxyphenyl)-4-phenyl-1-(E)-3-(E)-butadiene (**7b**)

Colorless plates; mp 64-65°C (n-hexane); yield: 59%; ms: m/z 266 (M^+); ^{1}H-nmr ($CDCl_3$): δ 3.83 (s, 6H, 2 X OCH_3), 6.39 (t, J = 2.2 Hz, 1H, 4-H-Ph), 6.61 (d, J = 2.2 Hz, 2H, 2,5-H_2-Ph), 6.60-6.71 (m, 2H, CH_a=CH_b-CH_c=CH_d), 6.90-6.99 (m, 2H, CH_a=CH_b-CH_c=CH_d), 7.24-7.45 (m, 5H, benzene H) ppm; Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.21; H, 6.53.

1-(3,4,5-Trimethoxyphenyl)-4-phenyl-1,3-butadiene (**7c**)

Colorless plates; mp 87-88°C (n-hexane); yield: 49%; ms: m/z 296 (M^+); ^{1}H-nmr ($CDCl_3$): δ 3.87 (s, 3H, 4-CH_3O-Ph), 3.91 (s, 6H, 3,5-$(CH_3O)_2$-Ph), 6.60 (d, J = 14.8 Hz, 1H, $(CH_3O)_3$-Ph-C**H**=CH-CH=CH-Ph), 6.67 (s, 2H, 2,6-H-Ph), 6.69 (d, J = 14.8 Hz, 1H, $(CH_3O)_3$-Ph-CH=CH-CH=C**H**-Ph), 6.87 (dd, J = 10.5 and 14.7 Hz, 1H, $(CH_3O)_3$-Ph-CH=C**H**-CH=CH-Ph), 6.95 (dd, J = 10.5 and 14.9 Hz, 1H, $(CH_3O)_3$-Ph-CH=CH-C**H**=CH-Ph), 7.22-7.45 (m, 5H, benzene H) ppm; Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.99; H, 6.91.

REFERENCES

1. C. A. Kingsbury and D. J. Cram, J. Am. Chem. Soc., 1960, **82**, 1810.
2. For example; B. M. Trost, T. N. Salzmann, and K. Hiroi, J. Am. Chem. Soc., 1976, **98**, 4887.
3. A. Ohta, K. Okimura, Y. Tonomura, M. Ohta, N. Yasumuro, R. Fujita, and M. Shimazaki, Heterocycles, 1988, **27**, 261.
4. A. Ohta, M. Shimazaki, N. Tanekura, and S. Hayashi, Heterocycles, 1983, **20**, 797.
5. V. B. Mahesh and T. R. Seshadri, J. Sci. Ind. Res., 1954, **13B**, 835.
6. Y. Asakawa, K. Tanikawa, and T. Aratani, Phytochemistry, 1976, **15**, 1057.
7. J. Buckingham, "Dictionary of Organic Compounds", 5th edition, Chapman and Hall, New York, 1982.
8. G. Butt and R. D. Topsom, Spectrochim. Acta, 1982, **38A**, 649.

9. N. Takamura, T. Mizoguchi, and S. Yamada, Chem. Pharm. Bull., 1975, **23**, 299.
10. R. L. Shriner and A. Berger, "Organic Syntheses", Coll. Vol. III, ed. by E. C. Horning, John and Sons, Inc., New York, 1955, p.786.
11. B. G. James and G. Pattenden, J. Chem. Soc., Perkin Trans. I, 1974, 1195
12. H. Güsten and M. Salzwedel, Tetrahedron, 1967, **23**, 173.
13. O. H. Wheeler and H. N. Batlle de Pabon, J. Org. Chem., 1965, **30**, 1473.
14. H. Güsten, L. Klasinc, V. Kramer, and J. Marsel, Org. Mass Spectrom., 1974, **8**, 323.
15. G. Billek, Fortschr. Chem. Org. Naturstoffe, 1964, **22**, 115.
16. H. Arichi, Y. Kimura, H. Okuda, K. Baba, M. Kozawa, and S. Arichi, Chem. Pharm. Bull., 1982, **30**, 1766.
17. K.-C. Luk, L. Stern, and M. Weigele, J. Nat. Prod., 1983, **46**, 852.
18. For example; 4-Hydroxystilbene: M.-F. Ruasse and J.-E. Dubois, J. Org. Chem., 1972, **37**, 1770. Resveratrol: M. Moreno-Manas and R. Pleixats, An. Quim., Ser. C, 1985, **81**, 157 [Chem. Abs., 1986, **105**, 133624q].
19. A. S. R. Anjaneyln, A. V. R. Reddy, D. S. K. Reddy, R. S. Ward, D. Adhikesavaln, and T. S. Cameron, Tetrahedron, 1984, **40**, 4245.
20. J. H. Pinchard, B. Will, and L. Zechmeister, J. Am. Chem. Soc., 1948, **70**, 1938.
21. M. Shimazaki, T. Nakanishi, M. Mochizuki, and A. Ohta, Heterocycles, 1988, **27**, 1643.

Received, 23rd February, 1989