+22.28° (c 5.03, pentane),[5] was prepared as previously described.[17] All the organoaluminum compounds were stored in sealed capillary glass vials in weighed amounts. The organoaluminum chlorides and bromides were prepared by the redistribution of the trialkylalanes with finely crushed anhydrous $AlCl_3$ and $AlBr_3$ in diethyl ether at 0 °C.[3b] The iodo compounds were prepared by adding a stoichiometric amounts of iodine in diethyl ether at 0 °C. The resulting alkyl iodide was removed by applying a reduced pressure to the reaction mixture.[3] Solvents were commercial reagent grade materials, purified by standard methods and redistilled under nitrogen from $LiAlH_4$ before use. GLC analyses were performed on a Perkin-Elmer 3920 B instrument with flame-ionization detectors and using 200 × 0.29 cm columns packed with 8% Carbowax 20M plus 2% KOH on 80–100-mesh Chromosorb W, while preparative GLC was carried out in a Perkin-Elmer F 21 chromatograph (300 × 0.80 cm columns, 8% Carbowax 20M plus 2% KOH on 80–100-mesh Chromosorb W). Optical rotations were measured with a Perkin-Elmer 142 polarimeter.

General Procedure. All reactions were carried out at least in duplicate under a dry nitrogen atmosphere. In a typical small-scale reaction, a three-necked, 25-mL, round-bottomed flask was fitted with a stirring bar, a glass stopcock, a Versilic silicone cap, and a sealed angular piece of glass tubing containing 4.13 mmol of $AlCl_3$. The vessel was charged with 10 mL of ether and cooled at 0 °C, and *i*-Bu_3Al (4.13 mmol) was added from the sealed capillary glass vial. The reaction flask was then turned so that the solid $AlCl_3$ dropped into the trialkylalane solution. After a 5-min agitation, isopropyl phenyl ketone (8.26 mmol) was injected by hypodermic syringe through the cap at the same temperature. The resulting mixture was stirred in a thermostated bath maintained at 0 °C for the desired time of aging. At intervals, samples of the mixture (0.4 mL) were withdrawn by a 500-μL hypodermic syringe and quenched in 10% H_2SO_4 solution (1 mL); quantitative (by the internal standard method) and qualitative analyses of the reaction products were performed by GLC on the crude mixture. All unknown products were isolated by preparative GLC, and their structures were deduced from ^1H NMR and mass spectra.

Asymmetric Reduction of Isopropyl Phenyl Ketone. The following procedure is representative of all the experiments. Isopropyl phenyl ketone (3.58 g, 24.16 mmol) in anhydrous diethyl ether (10 mL) was added rapidly at 0 °C to an ether solution (30 mL) of (*S*)-(2-methylbutyl)aluminum sesquichloride (prepared from 2.90 g, 12.08 mmol, of the trialkylalane and 1.61 g, 12.08 mmol, of $AlCl_3$) in a flame-dried, two-necked 100-mL flask. A yellow-orange coloration developed immediately and faded slowly. After 45 h the resulting mixture was cautiously hydrolyzed with dilute sulfuric acid, and the organic products were extracted with pentane. Preparative GLC purification afforded 1.92 g of (−)-(*S*)-1-phenyl-2-methyl-1-propanol [bp 104 °C (18 mmHg), $[\alpha]^{25}_D$ −9.53° (c 8.29, ether)[5]] and 0.91 g of (−)-(*S*)-1-phenyl-2-methyl-1-chloropropane: bp 97 °C (18 mmHg); $[\alpha]^{25}_D$ −0.92° (c 1.30, ether).[7]

(−)-(*S*)-1-Phenyl-2-methyl-1-chloropropane. (−)-(*S*)-1-Phenyl-2-methyl-1-propanol [1.87 g; $[\alpha]^{25}_D$ −14.64° (c 4.73, ether)[5]] was added dropwise with cooling (−20 °C) to freshly distilled thionyl chloride (6.70 g). The resulting mixture was stirred at room temperature for 3 h and then heated for 15 min on a steam bath. The excess thionyl chloride was removed under reduced pressure; the mixture was cautiously hydrolyzed with water, extracted with purified ether, washed with a dilute $NaHCO_3$ solution, and dried (Na_2SO_4). Removal of the solvent and distillation afforded (−)-(*S*)-1-phenyl-2-methyl-1-chloropropane: 1.91 g (91% yield); bp 97 °C (18 mmHg); $[\alpha]^{25}_D$ −14.14° (c 11.30, ether).[7]

A 5-mL solution of the chloride (0.337 g, 2.00 mmol) and $AlCl_3$ (0.047 g, 0.351 mmol) in diethyl ether, showed $[\alpha]^{25}_D$ −8.13° and −5.22° after 40 h and 98 h, respectively. A 5-mL solution of the chloride (0.629 g, 3.73 mmol) and (1-phenyl-2-methyl-1-propanoxy)aluminum dichloride (0.11 mmol), prepared 24 h before, in diethyl ether showed $[\alpha]^{25}_D$ −12.47° and −6.20° after 2 and 16 h, respectively.

(1-Phenyl-2-methyl-1-propanoxy)aluminum Dichloride. To a 10-mL ethereal solution of isobutylaluminum dichloride (7.37 mmol) was added slowly at 0 °C 1-phenyl-2-methyl-1-propanol (1.11 g, 7.37 mmol). The mixture was maintained at 0 °C for 24 h and then hydrolyzed with dilute sulfuric acid. GLC analysis showed the presence of 1-phenyl-2-methyl-1-chloropropane (51%) and 3-phenyl-2-methylprop-2-ene (48%).

Registry No. Isopropyl phenyl ketone, 611-70-1; (*S*)-1-phenyl-2-methyl-1-propanol, 34857-28-8; 2-methylbutene, 563-46-2; (*S*)-1-phenyl-2-methyl-1-chloropropane, 77482-02-1; 3-phenyl-2-methylprop-2-ene, 768-49-0; bis[(*S*)-2-methylbutyl]aluminum chloride, 17303-81-0; bis[(*S*)-2-methylbutyl]aluminum bromide, 17444-79-0; bis[(*S*)-2-methylbutyl]aluminum iodide, 77482-03-2; (*S*)-(2-methylbutyl)aluminum sesquichloride, 77482-39-4; (*S*)-(2-methylbutyl)aluminum sesquibromide, 77482-40-7; *i*-Bu_3Al, 100-99-2; *i*-Bu_2AlCl, 1779-25-5; *i*-Bu_2AlBr, 3551-72-2; *i*-Bu_2AlI, 691-94-1; *i*-$Bu_nAl_2Cl_3$, 12090-38-9; *i*-$Bu_3Al_2Br_3$, 12090-35-6; *i*-$BuAlCl_2$, 1888-87-5; *i*-$BuAlBr_2$, 13285-80-8.

(17) Pino, P.; Lardicci, L.; Lorenzi, G. P. *Ann. Chim. (Rome)*, 1958, *48*, 1426–1437.

Highly Stereoselective Route to (*E*)-Allyl Amines via Vinyltri-*n*-butylphosphonium Salts (Schweizer Reaction)

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The reaction of vinyltri-*n*-butylphosphonium salts, aldehydes, and sodiophthalimide in THF gave good yields of the allylic phthalimides with high *E* stereoselectivity (75–100%). The use of the vinyltriphenylphosphonium salts (Schweizer reaction) gave the allyl phthalimide with the *Z* isomer predominating. A study of the phthalimide cation and the effect of added lithium salt showed some reversal in the olefin geometry but in general the selectivity was only 3:1.

The preparation of allyl amines has been an area of considerable activity in recent years due primarily to their key position as synthetic intermediates, as well as their presence in various natural products. Our efforts to reach the antibiotic griseoviridin (1), whose synthetic strategy is based on the two key fragments **2** and **3**, required a route to allylic primary amines. The macrocyclic lactone **2** has already been successfully reached[1] and it remained only

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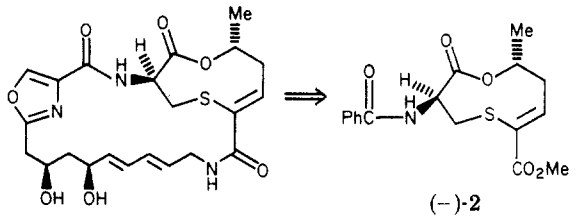
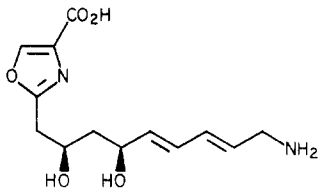


1[14] (−)-2



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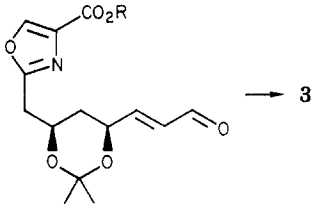
to fulfill our goal by reaching **3**. The problem then reduces down to a method of elongating a carbonyl derivative **4**[2] to the allyl amine. A survey of the literature reveals that



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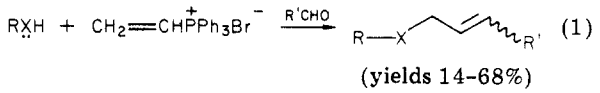
a number of reports have recently appeared dealing with the synthesis of allyl amines,[3] but each lacks either the appropriate substituent pattern, gives isomeric products or poor *E,Z* stereochemical ratios, or requires reaction conditions which are incompatible with our needs. The report by Schweizer[4] in 1966 which cleverly outlined a chain elongation of amines, alcohols, or thiols by adding them to vinyltriphenylphosphonium bromide and carbonyl compounds appeared to hold the key to a successful stereoselective allyl amine synthesis (eq 1).[5,6] Recently, Evans[7] has used the Schweizer method in the total synthesis of (±)-cheryline although no stereochemistry was involved.

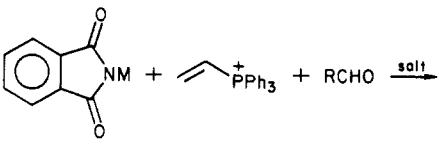


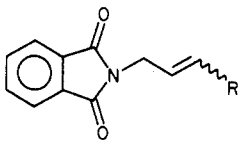
(1)

(yields 14-68%)

We now describe the results of a study which display the generality of the Schweizer reaction and provide for an efficient route to (*E*)-allyl amines in high stereochemical

Table I. Reaction of Phthalimide and Vinyltriphenylphosphonium Bromide with Aldehydes. Effect of Cation and Added Salts

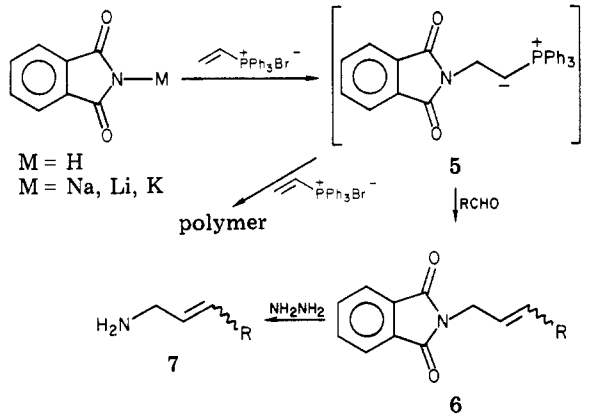




			N-allylphthalimide	
RCHO[a]	M^+	LiBr	% yield	% *E*:*Z*[c]
Ph	Na^+	none	61	27:73
Ph	Na^+	0.6 equiv	55	74:26
Ph	Li^+	none	32	74:26
Ph[b]	K^+	none	11	15:85
p-ClPh	Na^+	none	48	25:75
	Na^+	none	68	21:79[d]
	Na^+	0.6 equiv	78	62:38

[a] Reactions run in THF unless otherwise noted. [b] Reaction run in DMF. [c] Determined from the ^1H NMR spectrum[8a] (4-5-ppm region) of the allyl protons (see Experimental Section). [d] Recrystallization from hexane-toluene gave a 40% yield of *E,Z*:*E,E* diene in a 90:10 ratio.

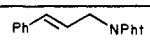
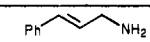
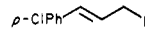
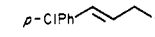
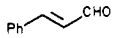
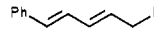
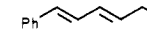
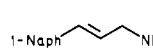
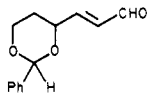
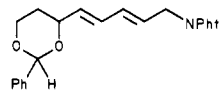
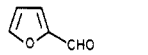
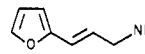
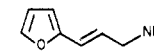
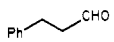
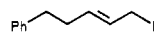
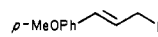
purity. Initially, we examined the use of phthalimide as a protected primary amine anion (Na^+, K^+, Li^+,) and added it to the vinyltriphenylphosphonium bromide admixed with the aldehyde. The yields of the allylic adducts **6** were poor, due mainly to polymerization of the initial Michael-type adduct **5** with the vinylphosphonium salt. However, when a suspension of sodium hydride, the vinylphosphonium salt, and benzaldehyde was treated with phthalimide in THF, respectable yields (48–78%) of the allylic imides, **6** (R = Ph), were obtained, but as a 73:27



mixture of the *Z*:*E* olefins, respectively. A number of additional experiments were carried out and these are summarized in Table I. These data describe the effects of varying the cation on the phthalimide, addition of LiBr[8] as a Lewis acid mediator, and investigation of three different aldehydes. Of particular significance was the reversal of the *E*:*Z* ratio when LiBr was added to the reaction mixture. Thus, with the sodium salt of phthalimide, the reaction gave, for all three aldehydes in Table I, approx-

(1) Meyers, A. I.; Amos, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 870.[14]
(2) Meyers, A. I.; Lawson, J. P., unpublished results.
(3) Mukaiyama, T.; Taguchi, T.; Nishi, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2797. Trost, B. M.; Keinan, E. *J. Org. Chem.* **1979**, *44*, 3451. Kakimoto, M.; Yamamoto, T.; Okawara, M. *Tetrahedron Lett.* **1979**, 623. Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901. German, C., Alexakis, A., Normant, J. F. *Tetrahedron Lett.* **1980**, 3763. Patel, B. A.; Heck, R. F.; *J. Org. Chem.* **1978**, *43*, 3898. Patel, B. A.; Dickerson, J. E.; Heck, R. F. *Ibid.* **1978**, *43*, 5018. Marxer, A.; Leutart, T. *Helv. Chim. Acta* **1978**, 61, 1708. Chaabouni, R.; Laurent, A.; Marquet, B. *Tetrahedron Lett.* **1976**, 757.
(4) Schweizer, E. E.; Smucker, L. D.; Votral, R. J. *J. Org. Chem.* **1966**, *31*, 467.
(5) Seyferth, Fogel, and Heeren (*J. Am. Chem. Soc.* **1964**, *86*, 307) reported the use of phenyllithium as a nucleophile to vinyltriphenylphosphonium bromide, affording the elaborated olefin.
(6) McIntosh and Khalil (*Can. J. Chem.* **1978**, *56*, 2134) also showed that Michael additions to vinyltriphenylphosphonium bromide can lead to a variety of heterocycles. For a review of this subject, see: Zibral, E. In "Organic Phosphorous Reagents in Organic Synthesis"; Academic Press: New York, 1979; pp 223–265.
(7) Hart, D. J.; Cain, P. A.; Evans, D. A. *J. Am. Chem. Soc.* **1978**, *100*, 1548.
(8) (a) Schlosser, M. *Top. Stereochem.* **1970**, *5*, 1. (b) House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin, Inc.: Menlo Park, CA, 1972; pp 701–709.

Table II. *N*-Allylphthalimides and (*E*)-Allyl Amines from Vinyl-*n*-butylphosphonium Bromide

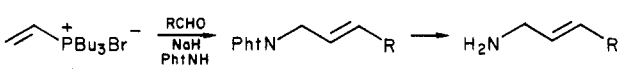
aldehyde	*N*-allylphthalimides (6) (% yield)	*E*:*Z*	(*E*)-allyl amines (7) (% yield)[b]
PhCHO	 (83)	100:0	 (83)
p-ClPhCHO	 (87)	100:0	 (78)
	 (95) (57)	83:17 100:0[a]	 (92)
1-NaphCHO	 (67) (50)	81:19 100:00[a]	
	 (43)	71:29	
	 (82) (70)	91:9 100:0[a]	 (78)
	 (78)	100:0	
	 (60)	75:25[c]	
p-MeOPhCHO	 (60) (50)	89:11 100:0[a]	

[a] Pure material obtained by a single crystallization (see Experimental Section). [b] Yield of amine based on starting aldehyde. [c] Determined by HPLC, see Experimental Section.

imately a 3–4:1 ratio favoring the *Z* olefin. Use of 0.6 equiv of LiBr to 1 equiv of the aldehyde reversed this result to 2–3:1 favoring the *E* olefin. Using the Li^+ salt of phthalimide gave mainly the *E* olefin (3:1) which was comparable to using the Na^+ salt and LiBr although in lower yields. The preponderance of the thermodynamically less favored *Z* olefin in the above study opens up a route to their preparation simply because a single recrystallization of the *Z*–*E* mixture gives the *Z*-enriched olefin in at least a 9:1 ratio (Table I, footnote *c*).

A further attempt to alter the *E*:*Z* ratio in the above reaction was made by examining the effect of solvent. Thus, benzaldehyde, the triphenylphosphonium salt, phthalimide, and NaH were mixed in various solvents (DMF, hexane, Et_2O). The *E*/*Z* ratios were relatively insensitive to solvent polarity or the chemical yields were too low to be useful, causing us to abandon this route.

The solution to our desired goal, namely, an efficient synthesis of (*E*)-allyl amines from the Schweizer method, was therefore still unanswered. There are reports[8] in the literature which describe variations in the Wittig reaction regarding *E*,*Z* product ratios, by varying the nature of the group on phosphorus (e.g., aryl vs. alkyl). With this in mind, we examined the potential of the tributylphosphonium salt 8.[9] When a suspension of the latter and



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sodium hydride in a solution of the aldehyde in THF was treated with solid phthalimide and the mixture allowed to stir at room temperature, an 83% yield of the allyl imide **6** which contained exclusively the *E* isomer was obtained. Thus, the tributylphosphonium salt was indeed the reagent of choice for reaching (*E*)-allyl amines in high isomeric purity. A number of aldehydes were examined under the same conditions and gave, in every case, the *E* isomer in ratios generally greater than 9:1. In those instances where the *Z* isomer was present (e.g., cinnamaldehyde) the 19% of the *Z* isomer could be quantitatively removed by a single recrystallization from ethanol (Table II, footnote *a*). It should be noted that several attempts to react the phthalimide anion and vinyltributylphosphonium salt with ketones (e.g., cyclohexanone, β-ionone) failed to give any allylic products under these conditions.

To reach the desired *E*-allylic amines, the allylic phthalimides were readily cleaved by using hydrazine[10] or Na_2S[11] followed by oxalic acid and gave the products in greater than 95% yield (Table II).

No explanation is offered at this time to account for the dramatic change in the Schweizer method in going from the triphenylphosphonium salt to the tributylphosphonium salt except to say that the thermodynamic product (*E* olefin) is undoubtedly favored by some transition-state orientation not observed with the triphenyl salt. These matters have been discussed by Schlosser[8] and will be considered further in the future.

Experimental Section

Vinyltri-*n*-butylphosphonium Bromide (8). The preparation is based on the patent[9] which was modified to produce the product on an ~100-g scale.

A mixture of 162 mL (0.65 mol) of freshly distilled tributylphosphine, 300 mL of dry 1,2-dimethoxyethane, and 48.4 mL (0.68 mol) of 2-bromoethanol (freshly distilled in vacuo) was heated to reflux for 4 days. When the tributylphosphine was completely gone (odor or ^1H NMR of an aliquot), 6 drops of 48% HBr and 243 mL (2.2 mol) of isopropenyl acetate (freshly distilled) were added and the mixture was heated at reflux for another 3 days (see below). The solvent and excess reagents were removed in vacuo leaving a thick yellow oil that slowly crystallized on standing. To the mass were added 400 mL of dry 1,2-dimethoxyethane and 68.9 g (0.65 mol) of finely ground sodium carbonate. The mixture was heated at reflux for 30–48 h (some frothing occurred) and then an aliquot was removed, evaporated, and dissolved in $CDCl_3$. The ^1H NMR spectrum showed the absence of the acetate methyl signal. The hot solution was filtered to remove the sodium salts and the solvent was removed in vacuo. The residue was triturated with 300 mL of ethyl acetate and allowed to stand, at which time crystalline material was slowly deposited. After collection by filtration, it was recrystallized from ethyl acetate–acetonitrile to

(9) Rouhut, M. M.; Borowitz, G. B.; Gillham, H. C. *J. Org. Chem.* **1963**, *28*, 2565. Keough, P. T.; Grayson, M. *Ibid.* **1964**, *29*, 631. These authors (Cyanamid group) describe the precursor to vinyltributylphosphonium bromide, namely, the (2-acetoxyethyl)tributylphosphonium bromide, but not the vinylphosphonium salt itself. In a later patent (*Chem. Abstr.* **1967**, *67*, 64527*t*) the vinyl salt is described.

(10) Ing, H. R.; Manske, R. H. F. *J. Chem. Soc.* **1926**, 2348.
(11) Kukolja, S.; Lammert, S. R. *J. Am. Chem. Soc.* **1975**, *97*, 5582.

give 110 g (57%) of colorless crystals: mp 149.5–150.5 °C (lit.[9] mp 151.5–152.5 °C); ^{1}H NMR ($CDCl_3$) δ 1.0 (m, 9), 1.6 (m, 12), 2.7 (m, 6), 6.1–7.3 (m, 3).

An alternative procedure for the preparation of the (2-acetoxyethyl)tri-*n*-butylphosphonium bromide, which is somewhat more convenient, follows. The dimethoxyethane solution of (hydroxyethyl)phosphonium salt was treated, instead of with the HBr–isopropenyl acetate reagent, with 46.2 mL of acetyl chloride and heated at reflux for 6 h. The solution was concentrated and the procedure continued as above.

General Procedure for Preparation of *E*-Allylic Phthalimides 6 from Vinyltri-*n*-butylphosphonium Bromide. In a dry 50 mL flask flushed with nitrogen was placed 1.5 mmol of 57% sodium hydride oil dispersion. The latter was washed (3×) with pentane, which was decanted away each time. THF was added (25 mL) and the suspension was then treated with 1.0 mmol of aldehyde, 1.3 mmol of vinyltributylphosphonium bromide, and finally 1.3 mmol of phthalimide. The entire mixture was stirred at 25–65 °C for 3–20 h, as specified for each compound, until TLC examination showed the absence of the aldehyde. Citric acid (5%) solution was added to destroy excess sodium hydride, the mixture was poured into water and extracted (3×) with ether, and the combined extracts were dried (K_2CO_3) and concentrated. The crude product was purified by preparative TLC (silica gel) using the indicated solvents or recrystallized. In some instances, the crude product was transformed directly to the free allylic amine.

(*E*)-1-Phenyl-3-phthalimido-2-propene, 6 (R = Ph), was prepared in 83% yield, following preparative TLC ($CHCl_3$–Et_2O–hexane, 5:1:4): R_f 0.4; mp 150–151.5 (lit.[12] mp 153–155 °C); ^{1}H NMR ($CDCl_3$) for pure *E* δ 4.51 (d, *J* = 6 Hz, 2), 6.30 (dt, *J* = 15.9, 6 Hz, 1), 6.6 (d, *J* = 15.9 Hz, 1), 7.(m, 5), 7.85 (m, 4). The *Z* isomer, obtained via vinyltriphenylphosphonium bromide (Table I) showed the following ^{1}H NMR spectrum ($CDCl_3$): δ 4.55 (dd, *J* = 6, 2 Hz, 2), 5.60 (dt, *J* = 12, 6 Hz, 1), 6.65 (dd, *J* = 12, 2 Hz, 1), 7.33 (m, 5), 7.80 (m, 4).

(*E*)-1-(4-Chlorophenyl)-3-phthalimido-2-propane, 6 (R = *p*-ClC_6H_4) was prepared in 87% yield following preparative TLC (silica gel, THF–Et_2O–hexane, 5:1:4): mp 172 °C (lit.[13] mp 171.5–172.5 °C); ^{1}H NMR ($CDCl_3$) δ 4.43 (d, *J* = 6, 2Hz, 2), 6.13 (dt, *J* = 16, 6 Hz, 1), 6.60 (d, *J* = 16 Hz, 1), 7.2 (br s, 4), 7.6–8.0 (m, 4).

Anal. Calcd for $C_{17}H_{12}NO_2Cl$: C, 68.58 H, 4.06. Found: C, 68.34; H, 4.26.

The *Z* isomer, obtained from vinyltriphenylphosphonium bromide (Table I), showed ^{1}H NMR ($CDCl_3$) δ 4.57 (dd, *J*= 0.8, 7 Hz, 2), 6.15–6.90 (m, 2), 7.15–8.0 (m, 8).

(*E*)-1-(4-Methoxyphenyl)-3-phthalimido-2-propene, 6 (R = *p*-$MeOC_6H_4$), was prepared by stirring the reaction mixture at 45 °C until TLC showed the absence of aldehyde. The yield was 60% after preparative TLC ($CHCl_3$–Et_2O–hexane, 5:1:4). The *E*:*Z* ratio from ^{1}H NMR was 89:11. Recrystallization from ethanol gave pure *E* isomer: mp 139.7–140.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3), 4.45 (d, *J* = 6 Hz, 2), 6.08 (dt, *J* = 16, 6 Hz, 1), 6.70 (d, *J* = 16 Hz, 1), 6.85 (d, *J* = 8 Hz, 2), 7.36 (d, *J* = 8 Hz, 2), 7.6–8.1 (m, 4).

Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15. Found: C, 73.50; H, 5.04.

(*E*)-1-(1-Naphthyl)-3-phthalimido-2-propene, 6 (R = 1-naphthyl), was prepared by stirring the reaction at 35 ° C until TLC showed no further aldehyde remaining. The yield was 67% following preparative TLC (silica gel, $CHCl_3$–Et_2O–hexane, 5:1:4). The *E*:*Z* ratio was 81:19 and recrystallization from dichloromethane–hexane gave pure *E* product: mp 124.5–125.0 °C; ^{1}H NMR ($CDCl_3$) δ 4.50 (d, *J* = 6.3 Hz, 2), 6.20 (dt, *J* = 15.4, 6.3 Hz, 1), 7.2–8.3 (m, 12).

Anal. Calcd for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.82. Found: C, 80.39; H, 4.71.

(2*E*,4*E*)-1-Phenyl-5-phthalimidopentadiene, 6 (R = PhCH=CH), was prepared by stirring the reaction mixture at 25 °C until TLC showed the absence of cinnamaldehyde. The yield was 95% after preparative TLC ($CHCl_3$–Et_2O–hexane, 5:1:4) as a 83:17 mixture of *E*,*E*/*E*,*Z* isomers (^{1}H NMR). The crude reaction mixture was recrystallized from absolute ethanol to produce pure *E*,*E* material in 57% yield: mp 160.0–161.5 °C; ^{1}H NMR ($CDCl_3$) δ 4.42 (d, *J* = 6 Hz, 2), 5.7–6.8 (m, 4), 7.4 (m, 5), 7.75 (m, 4).

Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.92; H, 5.12; N, 5.04.

4-(5-Phthalimido-2*E*,4*E*-pentadienyl)-2-phenyl-1,3-dioxane was prepared by reaction at 25 °C and gave the product in 43% yield after preparative TLC (silica gel, ethyl acetate–$CHCl_3$, 1:24). the *E*,*E*:*E*,*Z* ratio was determined by high-performance liquid chromatography (HPLC) to be 71:29, using a μ-Porasil column and 15% THF–isooctane. The peak separations were baseline and the detector was both 254 nm and refractive index. Both integrations led to the ratio of products observed. The R_f's of the two isomers were (*E*,*Z*) 6.3 min and (*E*,*E*) 7.2 min at 2.0 mL/min. The isomers were not separated into pure components. ^{1}H NMR of the mixture ($CDCl_3$): δ 1.5–2.2 (m, 2), 3.8–4.6 (m, 3), 4.22 (d, *J* = 6, 2 Hz, 2, *E*,*E* isomer), 4.35 (d, *J* = 6 Hz, 2, *E*,*Z* isomer), 5.3–7.2 (m, 4 H), 7.2–7.9 (m, 9). An elemental analysis of this mixture was not performed.

(*E*)-1-(2-Furyl)-3-phthalimido-2-propane, 6 (*r* = 2-furyl), was prepared by reaction at room temperature and gave the product in 82% yield after preparative TLC (Et_2O–hexane–dichloromethane, 6:3:1). The *E*:*Z* ratio was 91:9. Recrystallization from hexane–toluene gave colorless crystalline product in 70% overall yield: mp 133–135 °C; ^{1}H NMR ($CDCl_3$) δ 4.44 (d, *J* = 5.5, 2), 6.40–6.15 (m, 3), 7.25 (m, 1), 7.75 (m, 4).

Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38. Found: C, 71.06; H, 4.29.

(*E*)-1-(2-Pyridyl)-3-phthalimido-2-propene, 6 (R = 2-pyridyl), was prepared by reaction at room temperature in 78% yield after preparative TLC (ether–hexane–dichloromethane, 5:4:1). The ^{1}H NMR spectrum showed no trace of the *Z* isomer. Recrystallization for hexane–toluene gave off-white needles: mp 143.5–145.0 °C dec; ^{1}H NMR ($CDCl_3$) δ 4.53 (d, *J* = 4 Hz, 2), 6.6–8.6 (m, 10).

Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.99; H, 4.21. Found: C, 72.69; H, 4.54.

(*E*)-1-Phenyl-5-phthalimidopentene, 6 (R = 2-phenethyl), was prepared as above at 25 °C except for the fact that sodium hydride was the last reagent to be added to the reaction mixture. The product was obtained in 60% yield after preparative TLC (silica gel, ether–hexane, 6:4). The crude product, an oil, was purified by Kugelrohr distillation, 120–140 °C (0.005 torr), to give a colorless oil (40%); ^{1}H NMR ($CDCl_3$) δ 2.1–2.9 (m, 4), 4.20 (d, *J* = 5 Hz, 2), 5.40–5.79 (m, 2), 7.00–7.40 (m, 5), 7.5–7.9 (m, 4). Although the 60-MHz spectrum showed no separation of allylic protons, the 360-MHz spectrum showed a mixture of isomers. HPLC separation (THF–hexane, 0.025:1) gave the *E*:*Z* ratio as 75:25. The R_fs of these isomers were (*Z*) 14.5 min and (*E*) 16.0 min at a flow rate of 2.0 mL/min.

Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88. Found: C, 78.09; H, 5.69.

(2*E*,4*E*)-5-Phenylpentadienylamine, 7 (R = PhCH=CH). To a solution of 174 mg (0.60 mmol) of the corresponding phthalimide **6** (R = PhCH=CH) in 18 mL of absolute ethanol was added 60 μL (1.8 mmol) of 95% hydrazine. The mixture was heated at reflux for 4.5 h and then made acidic (pH ≥2) with concentrated hydrochloric acid. Heating was continued for an additional hour, and after cooling, the resulting suspension was removed by filtration. The filtrate was diluted with an equal volume of water and then washed with ether. The ether washings were discarded and the aqueous layer was rendered alkaline (pH ≥10) with solid potassium hydroxide. Extraction with ether (2×), combination of the ethereal fractions, drying (Na_2SO_4), and concentration gave 93 mg (97%) of the amine. The product was sublimed at 92 °C (0.01 torr) to give a colorless solid, mp 101–102 °C dec, which turned yellow on standing under vacuum in the presence of light. This behavior precluded any attempts at elemental analysis, although the amine could be stored under a nitrogen atmosphere in the dark for several days: ^{1}H NMR

(12) Gensler, W. J.; Rocket, J. C. *J. Am. Chem. Soc.* **1955**, *77*, 3262.
(13) Brewbaker, J. L.; Hart, H. *J. Am. Chem. Soc.* **1969**, *91*, 711.
(14) We have recently learned (B. Baum, private communication) that the structure of griseoviridin was incorrectly reported in the literature (Bycroft, B. W.; King, T. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1996; Birnbaum, G. I.; Hall, S. R. *J. Am. Chem. Soc.* **1976**, *98*, 1926) and is correctly represented as 1.

($CDCl_3$) δ 1.22 (br s, exchanges with D_2O, 2), 3.32 (br d, J = 6 Hz, 2), 5.60–7.05 (m, 4), 7.33 (m, 5); IR (film) 3622, 3352, 3165, 3015, 2900, 2836, 1635, 1592, 1488, 1447, 1379, 1297, 1070, 987, 850, 744, 690 cm^{-1}.

(*E*)-3-(*p*-Chlorophenyl)-2-propenylamine, 7 (R = *p*-ClC_6H_4), was obtained, as above, via hydrazine cleavage of the phthalimide, in 78% overall yield. In this instance, the crude phthalimide was used directly for the preparation. The allyl amine was sensitive to air, light, and atmospheric carbon dioxide which slowly transformed the oily product into a carbonate salt. However, freshly prepared amine could be spectroscopically characterized; ^1H NMR ($CDCl_3$) δ 1.50 (br s, 2), 3.50 (br s, 2), 6.32–6.72 (m, 2), 7.30 (s, 4). The broad singlet at δ 1.50 exchanged with D_2O.

(*E*)-3-(2-Furyl)-2-propenylamine, 7 (R = 2-furyl). The crude phthalimide **6** (R = 2-furyl) was dissolved in 50 mL of THF and 40 mL water and cooled to 0 °C in an ice bath. After 2.0 g of $Na_2S{\cdot}H_2O$ was added and the solution was stirred at 0 °C for 2 h, the mixture was made alkaline by addition of 3 mL of 50% sodium hydroxide. Extraction with ether (salt was added to facilitate the separation of layers) and discarding the ether wash gave an aqueous solution which was acidified (pH 1) with concentrated hydrochloric acid and extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and concentrated to leave a yellow solid (phthalamic acid).[11] The solid was dissolved in 70 mL of methanol and then 9 mL of saturated oxalic acid was added and the solution heated to reflux for 8 h. The cooled solution was acidified with 3 mL of concentrated hydrochloric acid and washed with dichloromethane. The aqueous layer was made alkaline with 50% sodium hydroxide (with cooling) and extracted with ether. After the solution was dried (Na_2SO_4), the solvent was removed, leaving a light yellow oil that was pure by ^1H NMR (78% yield). Kugelrohr distillation (110–120 °C, 20 torr) gave a colorless oil: ^1H NMR ($CDCl_3$) δ 2.45 (s, 2), 3.38 (d, J = 4 Hz, 2), 6.0–6.4 (m, 4), 7.25 (s, 1); IR (film) 3450, 1600 cm^{-1}. The product rapidly forms (~0.5 h) a solid when exposed to the atmosphere (carbonate salt).

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Registry No. (*E*)-**6** (R = Ph), 17480-07-8; (*Z*)-**6** (R = Ph), 4335-61-9; (*E*)-**6** (R = *p*-ClPh), 22621-98-3; (*Z*)-**6** (R = *p*-ClPh), 77629-04-0; (*E,E*)-**6** (R = PhCH=CH), 77629-05-1; (*E,Z*)-**6** (R = PhCH=CH), 77629-06-2; (*E*)-**6** (R = 1-naphthyl), 77629-07-3; (*Z*)-**6** (R = 1-naphthyl), 77629-08-4; (*E*)-**6** (R = *p*-$MeOC_6H_4$), 77629-09-5; (*Z*)-**6** (R = *p*-$MeOC_6H_4$), 77629-10-8; (*E*)-**6** (R = 2-furyl), 77629-11-9; (*Z*)-**6** (R = 2-furyl), 77629-12-0; (*E*)-**6** (R = 2-pyridyl, 77629-13-1; (*E*)-**6** (R = 2-phenethyl), 77629-14-2; (*Z*)-**6** (R = 2-phenethyl), 77629-15-3; (*E*)-**7** (R = Ph), 4335-60-8; (*E*)-**7** (R = *p*-ClPh), 60691-88-5; (*E,E*)-**7** (R = PhCH=CH), 77629-16-4; (*E*)-**7** (R = 2-furyl), 77629-17-5; **8**, 1883-19-8; 4-(5-phthalimidopentadienyl)-2-phenyl-1,3-dioxane, 77629-18-6; vinyltriphenylphosphonium bromide, 5044-52-0; benzaldehyde, 100-52-7; *p*-chlorobenzaldehyde, 104-88-1; (*E*)-3-phenyl-2-propenal, 14371-10-9; phthalimide sodium salt, 33081-78-6; phthalimide lithium salt, 51501-57-6; phthalimide potassium salt, 1074-82-4; 1-naphthalenecarboxaldehyde, 66-77-3; 2-furancarboxaldehyde, 98-01-1; 2-pyridinecarboxaldehyde, 1121-60-4; benzenepropanal, 104-53-0; 4-methoxybenzaldehyde, 123-11-5; 3-(2-phenyl-1,3-dioxan-4-yl)-2-propenal, 77629-19-7; phthalimide, 85-41-6.

Notes

New Synthesis of *s*-Triazolo[1,5-*a*]pyridines and *s*-Triazolo[5,1-*a*]isoquinoline

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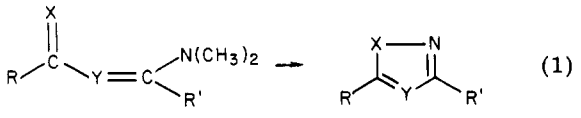
In previous publications,[1,2] we described a general method for the synthesis of 1,2,4-thiadiazoles **4**, isoxazoles **5**, and isothiazoles **6** (eq 1) in which the (dimethylamino)-

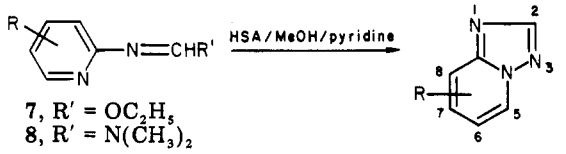


(1)

1, X = S; Y = N
2, X = O; Y = CH
3, X = S; Y = CH

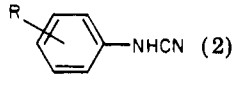
4, X = S; Y = N
5, X = O; Y = CH
6, X = S; Y = CH

alkylidene moiety was utilized as a masked acyl function.[1-6] The method involved the reaction of *N'*-(thioaroyl)-*N,N*-dimethylamidines **1**, enaminones **2**, and thioenaminones **3** with hydroxylamine-*O*-sulfonic acid (HSA) to give 1,2,4-thiadiazoles **4**, isoxazoles **5**, and isothiazoles **6** in excellent yields. We now report the extension of the method to the synthesis of *s*-triazolo[1,5-*a*]pyridines **9** and *s*-triazolo[5,1-*a*]isoquinoline (**12**) by the reaction of ethyl formimidates **7** and *N',N'*-dimethylformamidines **8** and **11** with HSA (eq 2 and 3).



7, R' = OC_2H_5
8, R' = $N(CH_3)_2$

9



(2)

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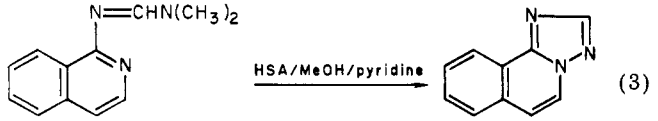

(3)

11 12

Ethyl formimidates **7**[7] and *N',N'*-dimethylformamidines **8** and **11**[8] were prepared in excellent yields by reported

(1) Lin, Yang-i; Lang, S. A., Jr. *J. Org. Chem.* **1980**, *45*, 4857.
(2) Lin, Yang-i, Lang, S. A., Jr.; Petty, S. R. *J. Org. Chem.* **1980**, *45*, 3750.
(3) Lin, Yang-i; Lang, S. A., Jr.; Lovell, M. F.; Perkinson, N. A. *J. Org. Chem.* **1979**, *44*, 4160.
(4) Lin, Yang-i; Lang, S. A., Jr. *J. Heterocycl. Chem.* **1977**, *14*, 345.
(5) Lin, Yang-i; Seifert, C. M.; Kang, S. M.; Dusza, J. D.; Lang, S. A., Jr. *J. Heterocycl. Chem.* **1979**, *16*, 1377.
(6) Lin, Yang-i; Lang, S. A., Jr. *Synthesis* **1980**, 119.
(7) Benko, P.; Pallos, L. *J. Prakt. Chem.* **1971**, *313*, 179.

0022-3263/81/1946-3123$01.25/0