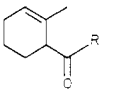
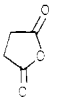
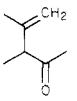
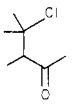
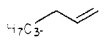
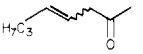
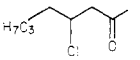
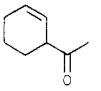
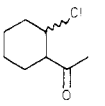
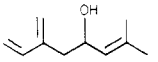
Table I. $EtAlCl_2$ Catalyzed Friedel-Crafts Acylation of Alkenes[a]

alkene	acylating agent	products (% yield)	
	CH_3COCl	a (54)	 a, R = CH_3; b, R = $(CH_3)_2C{=}CH$; c, R = Ph; d, R = $CH_2CH_2CO_2H$
	$(CH_3CO)_2O$	a (55)	
	$(CH_3)_2C{=}CHCOCl$	b (64)	
	$[(CH_3)_2C{=}CHCO]_2O$	b (60)	
	PhCOCl	c (40)[b]	
		d (20)[c]	4
	CH_3COCl	(53)  5	(13)  6
	$(CH_3CO)_2O$	(36)	(35)
	CH_3COCl	(65)[d]  7	(16)  8
	$(CH_3CO)_2O$	(21)[d]	(21)
	CH_3COCl	(73)  9	(16)[e]  10
	$(CH_3)_2C{=}CHCOCl$	(12)[c,f]  11	

[a] Reaction for 1 h in CH_2Cl_2 at 25 °C unless otherwise specified. [b] Propiophenone was isolated in 23% yield. [c] See Experimental Section for reaction conditions. [d] 70:30 *E-Z*. [e] 75:25 trans-cis. [f] Yield after reduction with $NaBH_4$.

saturated brine, dried ($MgSO_4$), and evaporated in vacuo (at 0 °C in the case of volatile products).

The spectral data for ketones **4a**,[6] **4b**,[9] **4c**,[17] **5**,[7] **6**,[18] **7**,[3b] **9**,[4] and **10**[12c] and alcohol **11**[19] are identical with those previously reported.

Enone 4a was purified by evaporative distillation (75 °C, 8 Torr).

Enone 4b was purified by evaporative distillation (70 °C, 0.1 Torr).

Enone 4c was purified by chromatography on silica gel with 9:1 hexane–ether as eluent. Propiophenone was also isolated in 23% yield.

Reaction with succinic anhydride was carried out in 15 mL of 1,2-dichloroethane for 16 h at room temperature. The reaction was quenched with water, dichloromethane, and 10% hydrochloric acid. The aqueous layer was separated and extracted twice with dichloromethane. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated to give 474 mg of an oil, which crystallized slowly. Recrystallization from petroleum ether gave pure **4d** as white needles (159 mg, 20%): mp 61–61.5 °C; NMR ($CDCl_3$) δ 5.67 (m, 1), 3.14 (m, 1), 2.55–3.0 (m, 4), 1.62 (s, 3), 1.4–2.2 (m, 6); IR (KBr) 2500–3500, 1707 cm^{-1}. Anal. (C, H).

The ratio of 5:6 was determined by analysis of the NMR spectrum. Evaporative distillation gave a mixed fraction (50 °C, 20 Torr), followed by pure **6** (75 °C, 14 Torr).

The ratio 7:8 was determined by analysis of the NMR spectrum and GC data. Pure samples were obtained by preparative GC. The data for **7** follow: NMR ($CDCl_3$) δ 3.15 (d, 0.3 × 2, J = 6 Hz, cis isomer[20]) and 3.08 (d, 0.7 × 2, J = 6 Hz, trans isomer[20]); GC t_R = 4.4 min (140 °C, 45 mL/min). The data for **8** follow: NMR ($CDCl_3$) δ 4.32 (tt, 1, J = 7 and 7 Hz), 2.93 (dd, 1, J = 8 and 16 Hz), 2.75 (dd, 1, J = 6 and 16 Hz), 2.19 (s, 3), 0.8–1.9 (m, 9); GC t_R = 12.2 min (140 °C, 45 mL/min).

The ratio of 9:10 and the stereochemistry of **10** was determined by analysis of the NMR spectrum and GC data. **9**: GC t_R = 8.0 min (140 °C, 40 mL/min). **10**: GC t_R = 22.1 min (140 °C, 40 mL/min).

Reaction of isoprene and dimethylacryloyl chloride was carried out for 1 h at −20 °C. Normal workup gave 526 mg of crude product. Sodium borohydride (0.19 g, 5 mmol) was added to a solution of this material (347 mg) in 2-propanol (15 mL) and water (5 mL). The solution was stirred for 4.5 h at 20 °C and poured into saturated brine. This mixture was extracted with 3 portions of pentane, which was dried (Na_2SO_4) and evaporated to give 328 mg of crude **11**. Chromatography on silica gel with 1:1 hexane–ether as eluent gave 47 mg (12%) of pure ipsdienol (**11**).

Acknowledgment. We thank the National Institutes of Health for generous financial support.

Registry No. **4a**, 15564-32-6; **4b**, 83632-87-5; **4c**, 32704-48-6; **4d**, 83632-84-2; **5**, 54678-04-5; **6**, 684-02-6; (*E*)-**7**, 37720-70-0; (*Z*)-**7**, 28362-73-4; **8**, 83632-85-3; **9**, 29372-98-3; *cis*-**10**, 83632-86-4; *trans*-**10**, 81568-11-8; **11**, 35628-00-3; $(CH_3CO)_2O$, 108-24-7; $(CH_3)_2C{=}CHCOCl$, 3350-78-5; $[(CH_3)_2C{=}CHCO]_2O$, 34876-10-3; PhCOCl, 98-88-4; $EtAlCl_2$, 563-43-9; CH_3COCl, 75-36-5; 1-methylcyclohexene, 591-49-1; 2-methyl-2-butene, 513-35-9; 1-hexene, 592-41-6; cyclohexene, 110-83-8; isoprene, 78-79-5; succinic anhydride, 108-30-5.

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Palladium-Catalyzed Synthesis of Cinnamylamines

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Received May 11, 1982

Cinnamylamines are useful intermediates in organic synthesis but as a class cannot be synthesized by one general procedure. We recently had need for a series of various substituted cinnamylamines and tried some of the

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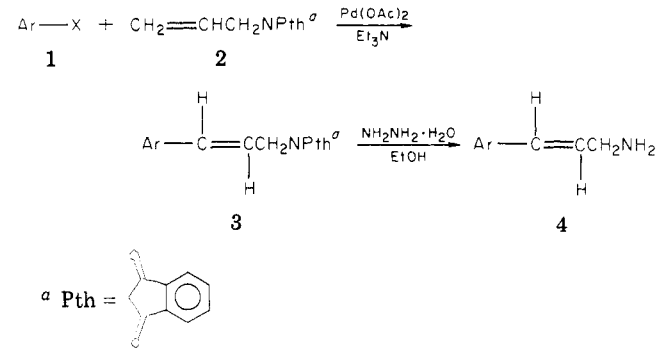
Scheme I



known methods. In a four-step synthesis, thermal rearrangement of an allylic trichloroacetimidic ester proceeded with poor yield.[1] Reduction of the appropriate nitrile with AlH_3[2] gave excellent yields of the amine but would be unuseable with groups not compatible with AlH_3. The syntheses of the nitriles not commercially available gave mixtures of cis and trans isomers and in some cases the Cannizzaro reaction predominated.[3]

Using Heck's method of oxidative addition of palladium to an aromatic halide and subsequent elimination, we found that $Pd(OAc)_2$ catalyzed this coupling in the key step[4-6] to give a short, high-yield, general synthesis of cinnamylamines as shown in Scheme I.

The diversity of the aromatic residues that can be used in the coupling is broad, from heterocycles to benzene rings containing multifunctional groups, as shown in Table I. The trans olefin was the only product detected and isolated, except in the case of reactants having an ortho substituent, as with 2-chlorobromobenzene. In the latter case, a mixture of cis and trans isomers was formed, which was separated by column chromatography. No reaction occurred when there were two ortho substituents, as with 2,6-dichlorobromobenzene, probably because of steric effects.

Electron-withdrawing and electron-donating groups on the aromatic ring had no apparent effect on the coupling. The exchangeable protons of phenol and aniline did not interfere in the reaction, and neither group needed protection. Several heterocycles were tried. Of the pyridine series only the 3-substituted pyridine yielded a product.[6] The 2-bromopyridine coupled to form bipyridyl, and the 4-bromopyridine gave no reaction, only recovered starting material. Bromopyrimidine and 2-amino-5-bromopyrimidine yielded products, as did furan and thiophene. The 2-thiophene and 3-thiophene yields reflect the stabilities of the starting bromides.

With $Pd(OAc)_2$ to catalyze the reaction, *N*-allylphthalimide (**1**) was coupled to an aromatic halide (**2**) in 2 equiv of triethylamine or 1 equiv of triethylamine and an equal volume of acetonitrile. The amine (**4**) was generated by refluxing 1 to 1.5 equiv of hydrazine hydrate with the phthalimide (**3**) in ethanol and monitoring the reaction by TLC. Alkaline workup and extraction with ether or methylene chloride afforded the amines in good yield. The products were homogeneous by TLC and NMR and were used without further purification.

The method affords a general synthesis of cinnamylamines, tolerating a multitude of functional groups, in good to excellent yields.[8]

Table I. Coupling of *N*-Allylphthalimide with an Aromatic Halide

Ar	X[a]	yield, % (anal.) 3	4[b]
C_6H_5	I	70 (ref 10)	–
p-Br-C_6H_4	I	58 (C, H, N, Br)	–
p-Cl-C_6H_4	I	70 (ref 10)	80 (ref 10)
o-Cl-C_6H_4	I	84[c]	74[d] (ref 11)
3,4-Cl_2-C_6H_3	I	80	80 (ref 12)
2,6-Cl_2-C_6H_3	Br	0	
p-Me_2N-C_6H_4	Br	50 (C, H, N)	70 (ref 12)
p-NO_2-C_6H_4	I	70	75
p-OH-C_6H_4	Br	68 (ref 13)	72[e] (ref 13)
3,4-(methylenedioxy)-C_6H_3	Br	60 (C, H, N)	58
p-(MeS)-C_6H_4	Br	78 (C, H, N, S)	56
4-NH_2-3-NO_2-C_6H_3	Br	95	–
4-MeOCO-C_6H_4	Br	70 (C, H, N)	77
4-CN-C_6H_4	Br	72 (C, H, N)	–
4-NH_2-C_6H_4	Br	52 (C, H, N)	–
3-thiophene	Br	71 (C, H, N, S)	96
2-thiophene	Br	21 (C, H, N, S)	83
5-MeOCO-furyl	Br	40	–
3-pyridyl	I	80	74[f]
2-pyridyl	Br	0	
4-pyridyl	Br	0	
5-pyrimidyl	Br	64 (C, H, N)	61
2-amino-5-pyrimidyl	Br	65 (C, H, N)	44

[a] When R = Br, 2 equiv of $(o\text{-tol})_3P$ to 1 of $Pd(OAc)_2$ was required; 1 mol % $Pd(OAc)_2$ was used per mole of halide. Yields were not optimized. [b] The synthesis of the specified amine with a (–) was not attempted. [c] Cis/trans ratio 1:6. [d] Based on the trans isomer. [e] Yield based on the phthalazinedione–amine complex isolated. [f] Yield based on isolated HCl salt.

Experimental Section

***N*-[4-(thiomethyl)cinnamyl]phthalimide.** *N*-Allylphthalimide (19.4 g, 0.103 mol), 4-bromothioanisole (20.3 g, 0.100 mol), and triethylamine (28 mL, 0.2 mol) were placed in a glass bomb with palladium acetate (224 mg, 0.001 mol) and tri-*o*-tolylphosphine (608 mg, 0.002 mol), flushed with nitrogen, then heated at 100 °C for 18 h with shaking. The solid residue was washed well with water, then recrystalized from hot DMF, filtering through Celite to remove the fine black precipitate (Pd^0). The hot DMF filtrate was diluted with an equal volume of water, after which crystalization occurred. The crystals were washed with water and then ethanol and suction dried: yield 24.0 g (78%). When an iodo starting material was used, the phosphine was omitted. Otherwise, this procedure was used in all cases.

4-(Thiomethyl)cinnamylamine. ***N*-[4-(Thiomethyl)cinnamyl]phthalimide** (6.2 g, 0.02 mol) and hydrazine hydrate (1.0 g, 0.02 mol) were refluxed in 75 mL of ethanol, until TLC

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(3) S. A. Dibiase, B. A. Lipisko, A. Haag, R. A. Wolak, and G. W. Gokel, *J. Org. Chem.*, **44**, 4640 (1979).
(4) J. E. Plevyak, J. E. Kickerson, and R. F. Heck, *J. Org. Chem.*, **44**, 4078 (1979).
(5) C. B. Ziegler and R. F. Heck, *J. Org. Chem.*, **43**, 2941 (1978).
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(7) K. L. Chung, F. G. Staken, B. A. Patel, and R. F. Heck, *J. Org. Chem.*, **47**, 1267 (1982).

(8) At the suggestion of one referee, allylamine was reacted with iodobenzene under the same reaction conditions. The iodobenzene was consumed, but only polymers were obtained.

monitoring indicated all the starting phthalimide was consumed. The solid (phthalazinedione–amine complex) was filtered, washed with ethanol, and then suspended in water to which 4 mL of 50% NaOH was added. After the mixture was shaken to dissolve all the solid, the oily product was extracted with two 100-mL portions of ethyl ether and one 100-mL portion of methylene chloride. The combined organic extracts were washed with water and dried over $MgSO_4$ and the solvent was removed in vacuo to yield 2.0 g (56%) of the product. Isolated as an oil, the product was homogeneous by TLC and NMR and was used without further purification.

This procedure was used in all cases. The water-soluble amines were extracted continuously overnight with methylene chloride. For all the compounds reported in Table I, the analytical data were consistent for the assigned structures. Elemental analyses were obtained for the indicated phthalimides and appear in the Supplementary Material (see paragraph at the end of paper concerning Supplementary Material). All were homogeneous by TLC and NMR. The cinnamylamines were needed and used as the free base and were reacted immediately upon isolation. All were homogeneous by TLC and NMR. The final products formed from the amines all gave satisfactory elemental and spectral data.[9]

Acknowledgment. We thank J. Pilney of the Department of Chemical Development for running the $Pd(OAc)_2$ bomb reactions.

Registry No. **2**, 5428-09-1; **3** (Ar = C_6H_5), 17480-07-8; **3** (Ar = *p*-BrC_6H_4), 83665-58-1; **3** (Ar = *p*-ClC_6H_4), 22621-98-3; (*E*)-**3** (Ar = *o*-ClC_6H_4), 83665-59-2; (*Z*)-**3** (Ar = *o*-ClC_6H_4), 83665-89-8; **3** (Ar = 3,4-$Cl_2C_6H_3$), 83665-60-5; **3** (Ar = *p*-$Me_2NC_6H_4$), 83665-61-6; **3** (Ar = *p*-$O_2NC_6H_4$), 83665-62-7; **3** (Ar = *p*-HOC_6H_4), 83680-96-0; **3** (Ar = 3,4-$(OCH_2O)C_6H_3$), 83681-26-9; **3** (Ar = *p*-$MeSC_6H_4$), 83665-63-8; **3** (Ar = 4-H_2N-3-$O_2NC_6H_3$), 83665-64-9; **3** (Ar = *p*-$MeOCOC_6H_4$), 83665-65-0; **3** (Ar = *p*-NCC_6H_4), 83665-66-1; **3** (Ar = *p*-$H_2NC_6H_4$), 83665-67-2; **3** (Ar = thiophene-3-yl), 83665-68-3; **3** (Ar = thiophene-2-yl), 83665-69-4; **3** (Ar = 5-$MeOC(O)C_4H_3O$), 83665-70-7; **3**·HCl (Ar = 3-pyridyl), 83665-71-8; **3** (Ar = 5-pyrimidyl), 83665-72-9; **3** (Ar = 2-amino-5-pyrimidyl), 83665-73-0; **4** (Ar = C_6H_5), 4335-60-8; **4** (Ar = *p*-BrC_6H_4), 83665-74-1; **4** (Ar = *p*-ClC_6H_4), 60691-88-5; **4** (Ar = *o*-ClC_6H_4), 83665-75-2; **4** (Ar = 3,4-$Cl_2C_6H_3$), 83665-76-3; **4** (Ar = *p*-$Me_2NC_6H_4$), 83665-77-4; **4** (Ar = *p*-$O_2NC_6H_4$), 83665-78-5; **4** (Ar = *p*-HOC_6H_4), 83665-79-6; **4** (Ar = 3,4-$(OCH_2O)C_6H_3$), 83665-80-9; **4** (Ar = *p*-$MeSC_6H_4$), 83665-81-0; **4** (Ar = 4-H_2N-3-$O_2NC_6H_3$), 83665-82-1; **4** (Ar = *p*-$MeOCOC_6H_4$), 83665-83-2; **4** (Ar = *p*-NCC_6H_4), 83680-97-1; **4** (Ar = *p*-$H_2NC_6H_4$), 83665-84-3; **4** (Ar = thiophen-3-yl), 83681-27-0; **4** (Ar = thiophen-2-yl), 83665-85-4; **4** (Ar = 5-$MeOC(O)C_4H_3O$), 83665-86-5; **4** (Ar = 3-pyridyl), 83665-87-6; **4** (Ar = 5-pyrimidyl), 83665-88-7; **4** (Ar = 2-amino-5-pyrimidyl), 83681-28-1; C_6H_5I, 591-50-4; *p*-BrC_6H_4I, 589-87-7; *p*-ClC_6H_4I, 637-87-6; *o*-ClC_6H_4I, 615-41-8; 3,4-$Cl_2C_6H_3I$, 20555-91-3; *p*-$Me_2NC_6H_4Br$, 586-77-6; *p*-$O_2NC_6H_4I$, 636-98-6; *p*-HOC_6H_4Br, 106-41-2; *p*-$MeSC_6H_4Br$, 104-95-0; 4-H_2N-3-$O_2NC_6H_3Br$, 875-51-4; *p*-$MeOCOC_6H_4Br$, 619-42-1; *p*-NCC_6H_4Br, 623-00-7; *p*-$H_2NC_6H_4Br$, 106-40-1; 3,4-$(OCH_2O)C_6H_3Br$, 2635-13-4; 3-bromothiophene, 872-31-1; 2-bromothiophene, 1003-09-4; 5-$MeOC(O)C_4H_3O$ bromide, 2527-99-3; 3-pyridyl iodide, 1120-90-7; 5-pyrimidyl bromide, 4595-59-9; 2-amino-5-pyrimidyl bromide, 7752-82-1.

Supplementary Material Available: Full NMR and selected elemental data for the compounds in Table I (6 pages). Ordering information is given on any current masthead page.

(9) The biological results of the final products have been presented; see "Abstracts of Papers", G. W. Adelstein, N. J. Malek, A. E. Moorman, D. G. Colton, and B. S. Pitzele, 183rd National Meeting of the American Chemical Society, Las Vegas, NV, Mar 28-Apr 2, 1982, American Chemical Society, Washington, DC, 1982, Abstr MEDI 61. The paper will be submitted to *J. of Med. Chem.*

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Reaction of Maleic Hydrazide with Diazomethane

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Received April 30, 1982

During derivatization studies on the growth regulator maleic hydrazide (for gas chromatography purposes), methylation with diazomethane was investigated. Maleic hydrazide behaves as a monobasic acid[1] and is thought to exist as structure 1A,[2] i.e., 6-hydroxy-3(2*H*)-pyridazinone, as opposed to structure 1B, i.e., 1,2-dihydro-3,6-pyridazinedione. Since diazomethane normally forms methyl ethers with weakly acidic hydroxy compounds such as enols, it was anticipated that the 6-hydroxy group would be preferentially methylated.

However, treatment of maleic hydrazide with an ethereal solution of diazomethane yielded significant amounts of three different compounds. Characterization of these compounds and subsequent studies indicated that the initial reaction gave both oxygen and nitrogen methylation with a substantial preponderance of the latter.

Results and Discussion

The major product (45%) from reaction of ethereal diazomethane with maleic hydrazide was readily identified by comparison of its properties with a known sample as 2-methyl-6-methoxy-3(2*H*)-pyridazinone (**3**).[3] Identification of a second reaction product (16%) as 6-methoxy-3(2*H*)-pyridazinone (**2**) was suggested by its nuclear magnetic resonance (NMR) and mass spectral (MS) data. Confirmation of this supposition followed treatment of the compound with diazomethane. Although only a small percentage (approximately 12%) was converted, the new product proved identical in all respects with the 2-methyl-6-methoxy analogue **3**.

The third (9%) and most interesting product from the reaction of maleic hydrazide with diazomethane exhibited extreme sensitivity (i.e., nanogram quantities) to gas chromatographic electron capture detection. This high sensitivity suggested the presence of strongly conjugated electrophores,[4] a situation that could exist only if the enedione system remained intact. MS data for the compound exhibited a molecular ion at m/e 82 above that for maleic hydrazide. The NMR spectra indicated the presence of three distinct methyl groups and one aromatic hydrogen. These properties suggested structure **8** (5,6-dihydro-1,5,6-trimethyl-1*H*-pyrazolo[3,4-*d*]pyridazine-4,7-dione) for the compound. The formation of **8** may be rationalized by assuming initial N-methylation of the 1 and 2 positions, followed by cycloaddition of diazomethane[5] across the 4,5 double bond (Scheme I). The pyrazoline intermediate **6** if thermally unstable could undergo intramolecular rearrangement and oxidation.[6] N-Methylation of the resultant pyrazole **7** would complete the sequence.

To help elucidate the reaction pathway for compound **8**, quantities of the presumed intermediates 2-methyl-6-hydroxy-3(2*H*)-pyridazinone (**4**)[2] and 1,2-dihydro-1,2-dimethyl-3,6-pyridazinedione (**5**) were prepared.[3] Treatment of compound **5** with diazomethane afforded **8** in good yields. Reaction of compound **4** with diazomethane also

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0022-3263/82/1947-5397$01.25/0 Published 1982 by the American Chemical Society