going on to products at a low rate) or whether this electron transfer is purely reversible and another slower path (direct one-step addition, e.g., via 3) leads from trans to product. The rapid isomerization with no net loss, however, is reminiscent of the situation proposed for the lack of reactivity of aldehydes and ketones[13] and certainly helps explain the unusual reactivity of $O_2^{-\cdot}$ toward S_N2 substrates. In the present case there is no really facile path available rather than reversal to 1, but for alkyl halides, production of peroxy radical and halide from the ET cage products could be efficiently competitive with reversal. Two recent publications presented convincing evidence for inversion of configuration at a normal 2° alkyl bromide in an electron transfer, radical process.[14] Further probes for this component should be examined in order to understand the chemical reactivity of this biochemically ubiquitous species.

Experimental Section

Materials. KO_2 (Alpha, 96.5%) is finely ground under N_2 and stored in a vacuum dessicator. 18-Crown-6 ether (Aldrich, CE) is purified as its acetonitrile complex. All solvents and anisole were fractionally distilled. Synthesis of 1[15] (~99% trans by GC and NMR) was followed by photoisomerization and partial crystallization (-78 °C) of trans from hexane solution, leaving a mixture predominantly *cis*-1 (typically 77% cis, 23% trans) which is then evaporated to dryness. NMR (T-60 in (Me_2SO-d_6), GC, and mp data are in accord with literature values (*trans*-1; δ 6.23, 6.90 (J = 9.5 Hz); *cis*-1, δ 5.67, 6.33 (J = 10 Hz)).

Methods. Analysis by GC is on a 6 ft × $^1/_8$ in. Carbowax 20M (10%) column at 100 °C (225 °C for stilbene), giving good isomer separations, with anisole as internal standard. For a typical run a small vial containing deaerated benzene (or other solvent), 1 (usually 0.2 M), anisole, CE, and a Teflon-coated stirring bar is placed in an argon-containing glovebag. Preweighed KO_2 is added, and the vial is serum-capped and removed from the glovebag. A microliter syringe is used to remove small samples for immediate GC injection from the continuously stirred solution. Nmr experiments are done under argon by filling a capped tube in an argon atmosphere glovebag immediately adjacent to the spectrometer.

Acknowledgment. We are grateful to Mr. Ken Feldman and Dr. Timothy Ungermann who began these experiments at U.C. Riverside. Sandra Russo was an NSF-URP participant.

Registry No. *cis*-1, 29569-89-9; *trans*-1, 20859-13-6; KO_2, 12030-88-5.

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Autoxidation of 1-(*tert*-Butylthio)-2-(*n*-propyl)isoindole

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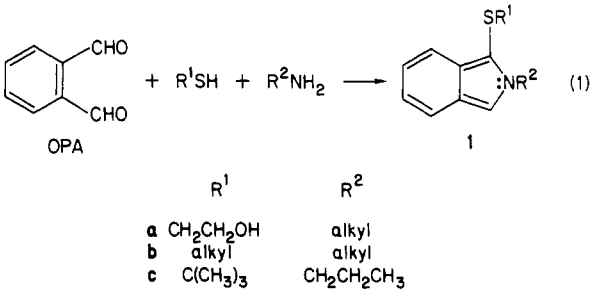
Received March 28, 1984

The fluorogenic reaction of *o*-phthalaldehyde (OPA) with primary amines in the presence of a thiol to produce intensely fluorescent 1-(alkylthio)-2-alkylisoindoles[1,2] 1 forms the basis for a sensitive analytical method specific for primary amines and primary amino acids.[3-8] These



	R^1	R^2
a	CH_2CH_2OH	alkyl
b	alkyl	alkyl
c	$C(CH_3)_3$	$CH_2CH_2CH_3$

1-thio-substituted isoindoles form a relatively new class of isoindoles for which only limited chemical information currently exists. Various alkyl (aryl) substituted isoindoles are known to be air-sensitive and undergo autoxidation,[9-14] but for the specific case of isoindoles bearing the 1-(2-hydroxyethyl)thio substituent the results of recent studies have shown that degradation occurs by nonoxidative processes that involve either intramolecular nucleophilic[1,15] or solvolytic attack[16] at C-1. It has not been determined whether these nonoxidative degradation pathways are an inherent property of 1-thio-substituted isoindoles or if they occur only with isoindoles bearing the 1-(2-hydroxyethyl)thio substituent, i.e., **1a**. Since these 1-thio-substituted isoindoles are rapidly gaining importance as analytically useful derivatives of primary amines and amino acids, the present work was undertaken to evaluate the reactivity of compounds of general structure **1b**. We now report the results of our investigation with a model compound of this class, 1-(*tert*-butylthio)-2-*n*-propylisoindole, **1c**.

When CH_3CN/H_2O (1:1, v/v) solutions of **1c** were exposed to air for 24 h, complete loss of the starting isoindole was observed by HPLC). Workup of a degraded solution followed by column chromatographic fractionation on silica gel and spectroscopic analysis (^{1}H NMR, low resolution MS, IR) resulted in the isolation and tentative identification of four degradation products as shown in Scheme II. 3-Hydroxy-2-*n*-propylphthalimidine (**2**) formed in 4% isolated yield, *N*-*n*-propylphthalimide (**3**), in 16% yield; 1,3-(di-*tert*-butylthio)-2-*n*-propylisoindole (**4**), 12% yield; and 3-(*tert*-butylthio)-2-*n*-propylphthalimidine (**5**), 35% yield. Degradation products **2** and **3** were confirmed from spectroscopic (^{1}H NMR, IR, MS) and chromatographic (TLC, silica gel; reversed-phase HPLC) comparisons to authentic samples prepared from literature procedures[9,17]

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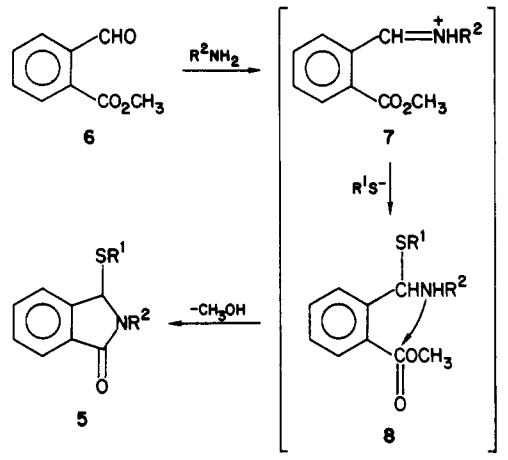
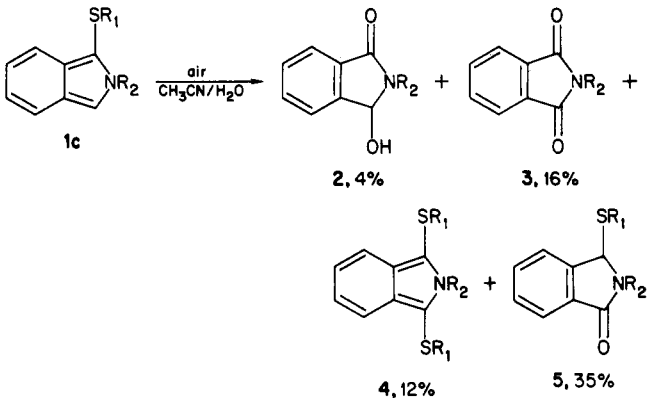
Scheme I. Synthesis of 3-(*tert*-Butylthio)-2-*n*-propylphthalimidine (5)[a]



[a] $R^1 = C(CH_3)_3$; $R^2 = CH_2CH_2CH_3$.

Scheme II. Degradation Products Formed from Aqueous Solutions of 1c[a]



[a] $R_1 = C(CH_3)_3$; $R_2 = CH_2CH_2CH_3$.

and from elemental analyses. Additionally, **4**, which has previously been reported as a degradation product,[15] was found to exhibit identical spectral and physical properties with those previously cited. The remaining major degradation product, **5**, is an unreported compound so an independent synthesis was devised to substantiate the structural assignment (Scheme I). The rationale for this synthetic approach is that aldehydes are known to react with amines in the presence of thiols to produce α-amino sulfides[18] (i.e., Scheme I, **6** → **7** → **8**). In the present case, the target compound, **5**, possesses the α-amino sulfide structural fragment. It was envisioned that by activating an *o*-carboxylic acid group to aminolysis (i.e., through esterification) the required intramolecular reaction would proceed readily (Scheme I, **8** → **5**). When methyl *o*-formylbenzoate (**6**), *n*-propylamine, and *tert*-butyl mercaptan were dissolved in THF and heated at reflux, the desired product, **5**, was obtained. Spectroscopic and chromatographic comparison of this synthetic product, **5**, with the isolated degradation product proved these materials to be identical, thus confirming the prior tentative identification. In addition all degradation products gave elemental analyses which corresponded to their assigned structures as shown in Scheme II.

Further characterization of the degradative process was undertaken by limited kinetic investigations in aqueous media. A sample, prepared with minimal exposure to oxygen and stored under argon, was subjected to various conditions. A portion was immediately placed in aqueous solution (0.01 M sodium tetraborate, ionic strength = 0.30 with 0.28 M sodium perchlorate), and the loss of **1c** and

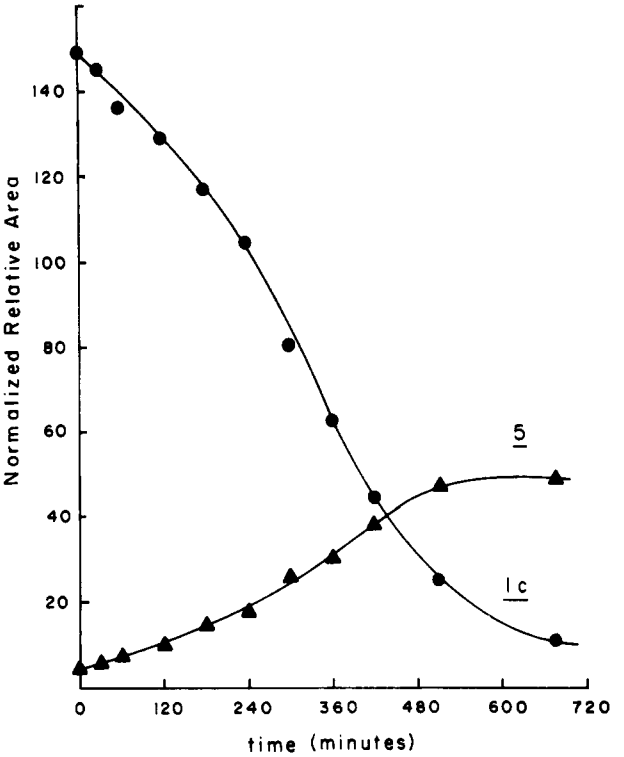


Figure 1. Degradation kinetics of **1c** determined on an oxygen-protected sample which was dissolved in aqueous solution and protected from light. Conditions: 10^{-5} M solution of **1c** prepared in 0.01 M sodium tetraborate, (μ = 0.30 M with 0.28 M sodium perchlorate, T = 40.5 °C, pH 8.95, pO_2 = 760 mm). The solution was protected from light < 500 nm and the reaction was monitored by HPLC.

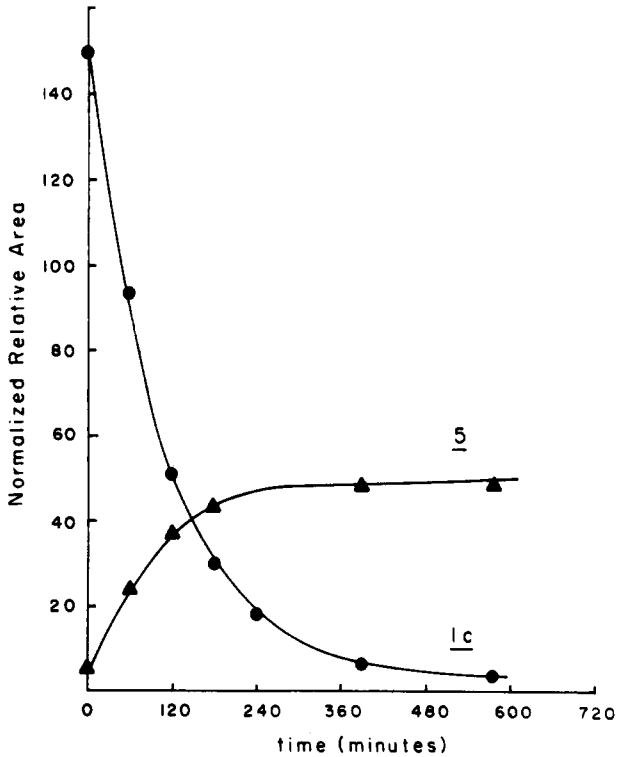


Figure 2. Degradation kinetics of **1c** exposed in the solid state to air at room temperature for 2.5 h prior to dissolution. Conditions and reaction media as described in Figure 1.

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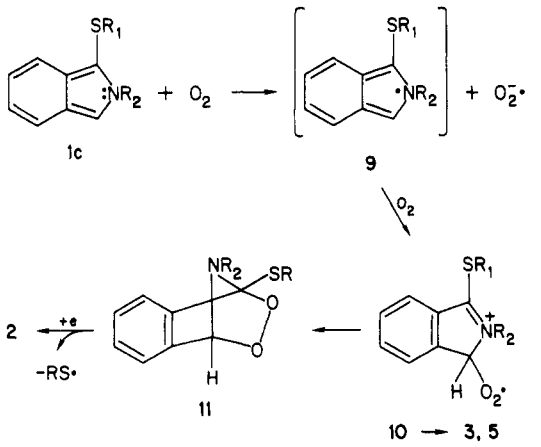
Scheme III. Mechanism Accounting for the Formation of Major Degradation Products of 1c Occurring via Oxidative Pathways



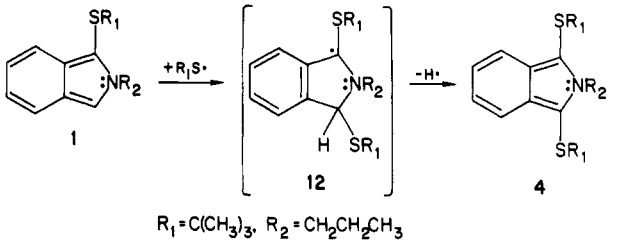
[a] $R_1 = C(CH_3)_3$; $R_2 = CH_2CH_2CH_3$.

formation of **5** were followed by reversed-phase HPLC (Figure 1). The second portion which was left exposed in the solid state to air at ambient temperature for 2.5 h and then treated exactly as in the previous sample exhibited a substantially different kinetic profile (Figure 2).

Despite the differing kinetic behavior exhibited by the two **1c** samples, in each case, the formation of the major degradation product, **5**, kinetically mirrored the loss of **1c** and was ultimately produced in equivalent (~44%) yield in each sample. These results together with the degradation product studies are both suggestive of an autoxidation process being responsible for loss of **1c** in aqueous solution. The sigmoid shaped curve for loss of **1c** (Figure 1) has been well established for other organic compounds which degrade via free-radical chain processes.[19] An autoxidation mechanism is further supported by the observation that exposure of **1c** to air, even while in the solid state, enhances the solution degradation rate (Figure 2), presumably by surface oxidation to species capable of serving as chain initiators. Degradation of **1c** was significantly retarded in the absence of O_2. Finally, the degradation products **3** and **5** are structurally similar to products produced from other non-thio-substituted isoindoles which are known to autoxidize.[9-14]

An autoxidation mechanism that accounts for three of the presently observed degradation products is presented in Scheme III. According to this mechanism, the extensively delocalized cation radical **9** is formed by electron transfer to oxygen or other radical species present,[9] thus initiating a chain process. Subsequently, **9** reacts with oxygen to form a key intermediate, the isoindoyl peroxy radical **10**, which can then react further by pathways previously postulated for isoindoles[10] including endoperoxide formation (**11**) accounting for the occurrence of the observed oxidative reaction products.

The nonoxidative degradation product, **4**, may be derived from reaction of thiyl radicals (produced during the oxidative process described in Scheme III) with intact parent isoindole via a homolytic substitution process through intermediate **12**. This type of reaction is well-known to occur with pyrroles[20,21] and would be expected to also take place with isoindoles due to the contribution from the resonance-stabilized intermediate produced during the reaction sequence.



$R_1 = C(CH_3)_3$, $R_2 = CH_2CH_2CH_3$

Undoubtedly, other mechanisms can be formulated to account for the observed products, but the present proposals are consistent with the features of previously established free-radical and isoindole chemistry and provide a congruent sequence to account for our observations.

In summary, from the present findings, it appears that generally 1-(alkylthio)-2-alkylisoindoles **1b** react similarly to other non-thio-substituted isoindoles with respect to autoxidation rather than being suspectible to the nonoxidative reactions at C-1 that were observed to occur with the more specialized case of the 1-[(2-hydroxyethyl)-thio]-2-alkylisoindoles **1a**.

Experimental Section

Melting points are uncorrected. Perkin-Elmer Model 727 and Varian Models FT-80A and F-60 spectrometers were used to acquire IR and ^1H NMR spectra, respectively. Mass spectra were obtained on a Varian CH-5 spectrometer using electron impact (70 eV) or chemical ionization (CI) modes. Elemental analyses were performed by the Department of Medicinal Chemistry, Universty of Kansas. The HPLC system consisted of a Waters Associates Model 6000A pump, U6K injector, Model 440 absorbance detector (254 mm), and a μ-Bondapak phenyl column (300 × 4.6 mm). Mobile phase: methanol/acetate buffer (50 mM; pH 5.7) in proportions of 65:35; flow rate 1 mL/min. Chromatographic peaks were quantitated with a Varian Model CDS-111L integrator. Solvents were either freshly distilled or of HPLC grade and *n*-propylamine (Aldrich Chemical Co.) was redistilled. All other chemicals were of reagant grade and used as received.

Synthetic Procedures. 1-(*tert*-Butylthio)-2-*n*-propylisoindole (1c). OPA (2.0 g, 0.015 mol) and *tert*-butyl mercaptan (1.35, 0015 mol) were dissolved in 95% MeOH (10 mL, argon saturated) and cooled to 0 °C. *n*-Propylamine (0.89 g, 0.015 mol) was added to the solution and an exothermic reaction ensued. Crystallization was induced by cooling (first in ice, then in dry ice/acetone). The solid was recovered by filtration under a stream of argon. The product was recrystallized 3× by rapid low-temperature crystallizations from argon-saturated MeOH. The product (1.13 g; 30% yield) was almost colorless and provided identical spectra and physical properties with those previously published.[15]

3-Hydroxy-2-*n*-propylphthalimidine (2). 3-Chlorophthalide and *n*-propylamine were reacted via an established procedure[17] to provide the desired product **2** in 54% yield, mp 90.5–92 °c (lit.[17] mp 92–93 °C). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.76; H, 7.00; N, 7.10.

***N*-*n*-Propylphthalimide (3).** Phthalic anhydride and *n*-propylamine were combined according to an existing procedure[9] to give the desired product **3** in 73% yield after recrystallization from $MeOH/H_2O$, mp 63.5–64.5 °C (lit.[22] mp 64.5 °C). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 70.00; H, 5.78; N, 7.28.

3-(*tert*-Butylthio)-2-*n*-propylphthalimidine (5). *tert*-Butyl mercaptan (7.21 g, 0.08 mol), *n*-propylamine (2.36 g, 0.04 mol) and methyl 2-formylbenzoate (3.28 g, 0.02 mol) were dissolved in THF (25 mL) and refluxed for 4 h. After removal of the solvent and volatiles under reduced pressure, a yellow liquid mixture (TLC, silica gel) was obtained. Fractionation by column chromatography (silica gel 60, hexane/ethyl acetate, 3/1) provided the desired product which crystallized upon standing. Recrystallization from hexanes gave a white solid of mp 45–46.5 °C. Anal.

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Calcd for $C_{15}H_{21}NOS$: C, 68.40; H, 8.04; N, 5.32. Found: C, 68.10; H, 8.20, N, 5.00. IR (KBr) 2960, 2930, 2870, 1690, 1615, 1465, 1395, 1360, 1315, 1210, 1160, 1065, 885, 865, 760, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.77–2.06 (t, s, m, 14 H), 3.16–4.23 (m, 2 H), 5.48 (s, 1 H), 7.23–7.90 (m, 4 H). EIMS (70 eV), *m/e* (relative intensity) 207 (M – isobutylene, 19), 174 (M – $SC(CH_3)_3$, 100), 132 (M – $SC(CH_3)_3$ – propylene, 47).

Acknowledgment. This work was supported in part by NIH Grant CA-09242 from the National Cancer Institute and is taken in part from the Doctoral Thesis by John F. Stobaugh entitled "Chemical Studies in the Fluorogenic Reaction of *o*-Phthalaldehyde with Primary Amines", University of Kansas, 1982.

Registry No. 1c, 64807-91-6; 2, 33125-70-1; 3, 5323-50-2; 4, 66161-45-3; 5, 91948-93-5; 6, 4122-56-9; OPA, 643-79-8; $PrNH_2$, 107-10-8; *t*-BuSH, 75-66-1; 3-chlorophthalide, 6295-21-2; phthalic anhydride, 85-44-9.

Trifluoroacetic Acid Catalyzed Allylic Phenylation of α-Methylallyl Acetate, α-Methylallyl Trifluoroacetate, and α-Methylallyl Alcohol with Benzene

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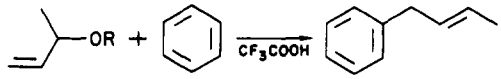
Received April 25, 1984

In a previous paper we have reported that the reaction of allyl esters with benzene in the presence of $Pd(OAc)_2$ and CF_3COOH gives cinnamaldehyde derivatives via the acyl–O bond fission–phenylation.[1] In connection with this reaction we have found that CF_3COOH without palladium salts causes phenylation of allylic esters and alcohol with benzene. This paper reports the CF_3COOH-catalyzed allylic phenylation of allyl compounds like α-methylallyl acetate, α-methylallyl trifluoroacetate, and α-methylallyl alcohol with benzene to give *trans*-1-phenyl-2-butene (1) in fair to good yields.



1

R = H, $COCH_3$, $COCF_3$

Allylic phenylation takes place by stirring the mixture of the allylic compound, CF_3COOH, and benzene at 80 °C. For example, the reaction of α-methylallyl trifluoroacetate with benzene in the presence of CF_3COOH at 80 °C gives 1 in a 78% yield together with 1-phenyl-1-butene (2) (3%) and 3-phenyl-1-butene (3) (1%) (run 5). The results are listed in Table I.

As is apparent from Table I, the trifluoroacetate (runs 3 and 5) is more reactive than the corresponding acetate (runs 1 and 2) and alcohol (run 6). In the case of α-methylallyl trifluoroacetate, the reaction proceeds even at room temperature (run 4). Substitution of CH_3COOH resulted in no reaction.

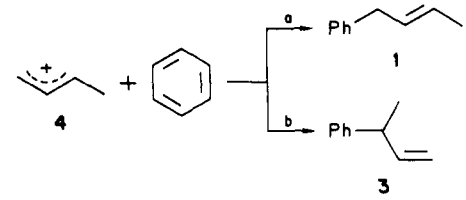
The role of CF_3COOH appears to be to convert the allylic acetate or alcohol to the trifluoroacetate and may further assist in dissociation to an allyl cation 4.[2] Electrophilic attack of 4 at C_1 (path a) or C_3 (path b) to benzene gives 1 or 3, respectively (Scheme I).[3] The almost exclusive formation of the 1-isomer may be due to the less sterically crowded position at C_1 in 4 and the less reactive nonpolar benzene substrate as compared to the usual solvolysis conditions. Addition of $Pd(OAc)_2$ to this reaction gave similar results.[1]

Table I. Allylic Phenylation with Benzene[a]

run	allylic compd, mmol	CF_3COOH, mL	temp, °C	time, h	yield of 1,[b] %
1	α-methylallyl acetate, 2.1	1.3	80	4	33[c]
2	α-methylallyl acetate, 2.0	0.5	80	8	21[d]
3	α-methylallyl trifluoroacetate, 1.6	1.3	80	8	64[e]
4	α-methylallyl trifluoroacetate, 1.6	1.3	rt[i]	53	16[f]
5	α-methylallyl trifluoroacetate, 1.5	0.8	80	8	78[g]
6	α-methylallyl alcohol, 2.0	0.5	80	8	21[h]

[a] Benzene, 5 mL. [b] Based on the starting allyl compound and determined by GLC. [c] A 1% yield of 3 and a trace amount of 2 were also formed. [d] A 1% yield of 3 was also formed. [e] A 2% yield of 2 and a 1% yield of 3 were also formed. [f] Trace amounts of both 2 and 3 were also formed. [g] A 3% yield of 2 and a 1% yield of 3 were also formed. [h] A 1% yield of 3 was also formed. [i] Room temperature.

Scheme I



The reaction described here is the first example of the allylic phenylation of allylic compounds with benzene by the catalysis of CF_3COOH and provides a very convenient route to 1.

Experimental Section

General Methods. NMR spectra were obtained with a Hitachi R-24S spectrometer using Me_4Si as an internal standard. The starting trifluoroacetate was prepared by treatment of α-methylallyl alcohol with trifluoroacetic anhydride: ^1H NMR (CCl_4) δ 1.46 (d, J = 7 Hz, 3 H, methyl), 5.10–6.20 (m, 4 H, allylic and olefinic).

General Method for Allylic Phenylation. Into a 50-mL centrifuge tube containing a magnetic stirring bar were added benzene (5 mL), the allyl compound, and CF_3COOH (see Table I), and the tube was sealed under air with a serum cap. Then the mixture was heated with stirring at 80 °C. After the usual workup, the products were analyzed and separated by GLC (Apiezon L, 1.5 m) to give 1 with 2 and 3 as byproducts. The identities of the products were proved by IR, NMR, and retention time comparison with samples prepared from dehydrations of 4-phenyl-2-butanol (compound 1) and 1-phenyl-1-butanol (compound 2) and from crotyl chloride and phenylmagnesium bromide (compound 3).[4] **1-Phenyl-2-butene (1)**: ^1H NMR (CCl_4) δ 1.50–1.81 (d, J = 5 Hz, 3 H, methyl), 3.08–3.40 (m, 2 H, allylic), 5.22–5.68 (m, 2 H, olefinic), 6.83–7.31 (m, 5 H, Ar). **1-Phenyl-1-butene (2)**: ^1H NMR (CCl_4) δ 1.10 (t, J = 7 Hz, 3 H, methyl), 2.10 (m, 2 H, allylic), 6.08–6.32 (m, 2 H, olefinic), 7.18 (s, 5 H, Ar).

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