SNAAP Sulfonimidate Alkylating Agent for Acids, Alcohols, and Phenols[1]

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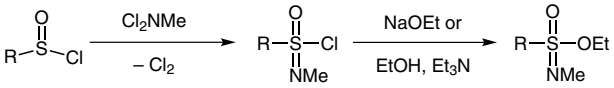
Abstract: Stable, crystalline ethyl *N-tert*-butyl-4-nitrobenzenesulfonimidate has been prepared in high yield by direct O-ethylation of *N-tert*-butyl-4-nitrobenzenesulfonamide with iodoethane and silver(I) oxide in dichloromethane. This sulfonimidate directly ethylates various acids to esters; the stronger the acid, the faster it alkylates and in higher yield. It readily ethylates alcohols and phenols to ethers at room temperature in the presence of tetrafluoroboric acid catalyst without molecular rearrangements or racemization. We have defined these reactions as SNAAP alkylations: [*s*ubstitution, *n*ucleophilic of *a*cids, *a*lcohols and *p*henols]. The *hard* sulfonimidate alkylating agent is chemoselective, preferring oxygen > nitrogen > sulfur. The sulfonamide byproduct of alkylation is readily recycled to the sulfonimidate.

Key words: mild alkylation, mild esterification, esters, ethers, sulfonimidate

There are a variety of methods for direct alkylation of carboxylic acids at oxygen, but many have limitations because of toxicity, thermal instability, reactivity with moisture in air, multiple components, severe conditions, or extended reaction times. A recent review by Vorbruggen[2] focused on the alkylation of carboxylic acids and phenols with amide acetals. He noted that classical procedures involving sterically hindered tetrahedral intermediates limit the scope of those procedures. Additionally, some direct alkylation methods, such as the toxic and explosive diazoalkanes,[3,4] also undergo side reactions with aldehydes, ketones and α,β-unsaturated carbonyl compounds.[5] Amide acetals are effective alkylating agents for many carboxylic acids and some acidic phenols,[2] but they are sensitive to water, alcohols, and amines, and easily condense with active methylene groups. Yoshino et al.[6] reported an improved esterification procedure for various carboxylic and phosphonic acids and other protic compounds with excess trialkyl orthoacetates in ionic liquids at 80 °C. Raber et al.[7] reported the alkylation of carboxylic acids with trialkyloxonium salts, but the literature is silent on the use of oxonium salts to alkylate strong acids, such as methanesulfonic and trifluoroacetic acids. Alkylation of alcohols directly, without first having to convert them into alkoxides,[8] is not common. Acid-catalyzed methylation of alcohols by the use of diazomethane and concentrated aqueous tetrafluoroboric acid gives methyl ethers.[9] The alkylation of alcohols by oxonium salts[10] requires reaction at room temperature for one week. Benzyl, allyl, and *tert*-butyl trichloroacetimidates have been shown to alkylate acids and alcohols under limited conditions[11–16] without chemoselectivity.[17]

There are limited previous reports of sulfonimidate reactions with carboxylic acids and hydrochloric acid[18,19] and fluorosulfonic acid;[20] multistep syntheses of sulfonimidates[18,19] are tedious, often resulting in unstable liquid products. As a result, alkylations by sulfonimidates are, to the best of our knowledge, unexplored. The N-alkylation of sulfonamides is well documented;[21–24] however, no practical method for direct O-alkylation of sulfonamides has been reported. Sulfonimidates, the products of O-alkylation, have been prepared previously by less direct, multistep methods (Scheme 1).[18,19,20,25,26] Most of these methods required sulfinyl chloride[25] and sulfonimidoyl chloride precursors, which were combined with alkoxides or alcohols and triethylamine in situ.[18,19,27,28] Reggelin and co-workers have reported[29] extensively on chiral cyclic sulfonimidates prepared from sulfonimidoyl chlorides.



Scheme 1 Sulfonimidates from sulfonimidoyl chlorides

In an earlier report,[30] we presented evidence that *N*-alkoxybenzenesulfinamides could rearrange to alkyl sulfonimidates and alkylate alcohols in situ. Malacria et al.[31] utilized this concept for their one-pot synthesis of sulfonimidates from sulfinamides, iodosobenzene, and primary aliphatic alcohols. A more recent paper on this work[32] includes asymmetric syntheses of sulfonimidates. Each of these methods required sulfinyl chlorides or sulfinamides derived from them, thus they were restricted to derivatives compatible with chlorine and required several steps. Roy showed that phenyl and 2,2,2-trifluoroethylsulfonimidates could be prepared from various N-silylated sulfonamides.[26] The sulfonimidoyl chloride intermediates were prepared from sulfonamides with triphenylphosphine dichloride and triethylamine, then converted with the alcohol and triethylamine into sulfonimidates in 10–78% yields. In many cases, the alkyl sulfonimidates reported

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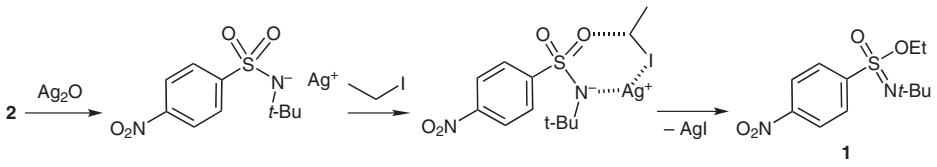
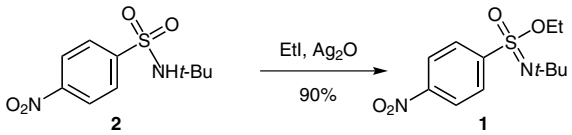


Scheme 2 Proposed mechanism for O-ethylation of sulfonamide

were unstable liquids at room temperature, with limited stability in a freezer.[20]

O-Alkylation of carboxylic amides gives imidates via their silver salts and alkyl iodides.[33–35] Control of reaction variables alters the regiochemistry, favoring O- versus N-alkylation. Challis and Iley[20] applied this approach to sulfonamides, but only obtained N-alkylation in acetonitrile. They concluded that: '*O*-alkyl sulphonimidates are unlikely to be synthesized by direct O-substitution.'

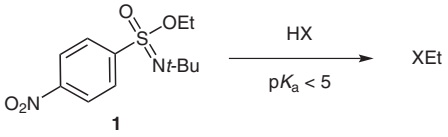
We have successfully accomplished the preparation of ethyl *N*-*tert*-butyl-4-nitrobenzenesulfonimidate (**1**) (Equation 1) by silver oxide mediated O-ethylation of *N*-*tert*-butyl-4-nitrobenzenesulfonamide (**2**). The best method we developed is a one-pot procedure involving anhydrous silver(I) oxide, iodoethane, and a sterically hindered sulfonamide, such as **2**, in anhydrous, refluxing dichloromethane. Stable, crystalline **1** has been prepared in ca. 90% yield by this method. N-Ethylation is a minor side reaction. This method applies generally to other arenesulfonimidates, but these were not included here, because they are unstable liquids at ambient temperature.



Equation 1 Direct sulfonamide to sulfonimidate synthesis

We have proposed a mechanism that begins with proton abstraction by silver(I) oxide to produce an ambident silver sulfonamide tight ion-pair, which is capable of attacking the iodoethane with competition between the oxygen and nitrogen nucleophilic sites (Scheme 2). Consistent with *h*ard and *s*oft *a*cid and *b*ase theory (HSAB),[36] the soft silver(I) cation should reside at the softer nitrogen basic site. Attack by nitrogen on the iodoethane may be sterically hindered both by the tightly complexed silver ion and the *N*-*tert*-butyl group. O-Ethylation of the silver sulfonamide may be a concerted nucleophilic attack by oxygen on the iodoethane carbon with loss of silver iodide. We note that O-ethylation (kinetic path) is favored in dichloromethane over N-ethylation (thermodynamic path) in acetonitrile. Most likely, this is because dissociation of the silver sulfonamide tight ion-pair may occur in polar solvents like acetonitrile, and loss of the silver ion could decrease steric hindrance at nitrogen.

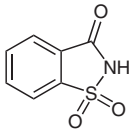
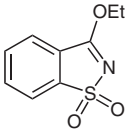
Stable, crystalline sulfonimidate **1** (Aldrich Cat. #L512311) represents a special class of alkylating agent; reactions with acids, alcohols and phenols are very simple, fast, and safe. Isolation of the resulting products is very direct. We have formulated the term SNAAP for the process, which is an acronym for *s*ubstitution, *n*ucleophilic of *a*cids, *a*lcohols, and *p*henols.



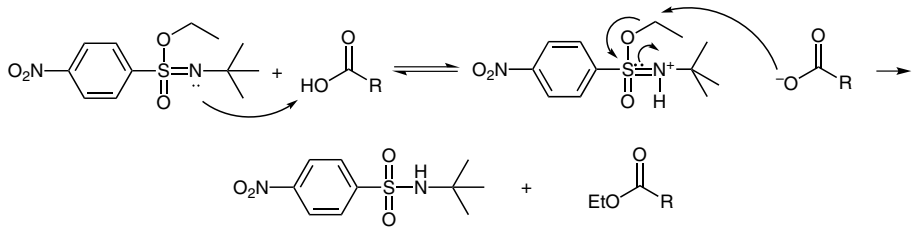
Equation 2 Sulfonimidate ethylation of acids

We have demonstrated the ethylation of a wide variety of acids [pK_a <5] (Equation 2) with **1** (Table 1) at ambient temperature. The stronger the acid, the faster the ethylation reaction proceeds. Methanesulfonic acid (entry 1)

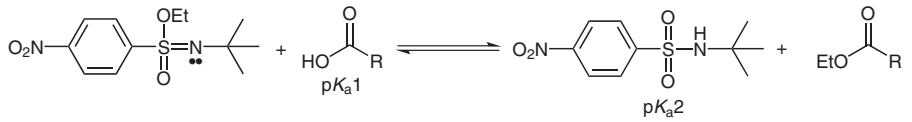
Table 1 Uncatalyzed Sulfonimidate Ethylation of Acids

Entry	Acid	pK_a	Time	Product	Yield (%)
1	$MeSO_2OH$	–1.9	15 min	$MeSO_2OEt$	89[a]
2	TFA	0.0	<5 min	CF_3CO_2Et	100[b]
3	Cl_2CHCO_2H	1.35	<5 min	Cl_2CHCO_2Et	58[a]
4	4-$MeC_6H_4S(O)OH$	1.99	<50 min	4-$MeC_6H_4S(O)OEt$	74[a]
5		2.2	2.5 h		46[a]

[a] Isolated yield.
[b] Yield was determined by NMR after removal of sulfonamide byproduct **2**.



Scheme 3 Proposed mechanism of proton-promoted sulfonimidate ethylation of acids



Scheme 4 Acid vs. sulfonamide pK_a affects reactivity

gave ethyl methanesulfonate in high yield in less than 5 minutes. 4-Toluenesulfinic acid (entry 4) gave exclusively the hard product, ethyl 4-toluenesulfinate,[37] by O-ethylation. No soft, S-alkylation to give ethyl 4-methylphenyl sulfone was detected. Saccharin (entry 5) was O-ethylated directly by **1** in 2.5 hours to give 3-ethoxy-1,2-benzthiazole 1,1-dioxide. The isolated product spectra are identical to the IR, NMR, and MS of authentic samples. In each case, the sulfonamide byproduct **2** was easily recovered and used to resynthesize the sulfonimidate **1**. The proposed mechanism is shown in Scheme 3.

Carboxylic acids with pK_a values ranging from 2.85 to 4.29 required refluxing in tetrahydrofuran for two to five days to obtain modest to good yields of the ethyl esters (Table 2). Salicylic acid (entry 2) and mandelic acid (entry 4) were chemoselective, alkylating only the acid. We attempted to accelerate sulfonimidate **1** esterification of benzoic acids (entries 1, 3, 5, and 6) using tetrafluoroboric acid dimethyl ether, but were unsuccessful; after one hour at room temperature, the sulfonimidate decomposed, with no significant production of ethyl benzoates.

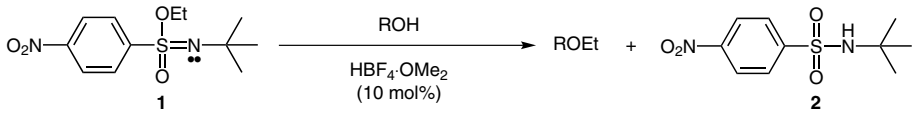
As a general rule, uncatalyzed ethylation of strong acids with lower pK_a values occurs faster, probably because of a higher concentration of the protonated sulfonimidate intermediate. The best alkylation conversions (Scheme 4) were accomplished when pK_{a2} of the sulfonamide was higher than pK_{a1} of the acid being alkylated. This best explains why salicylic (2.97) and mandelic (3.85) acids were ethylated on the carboxyl groups without affecting the hydroxy groups. This may be because the pK_{a2} of the sulfonamide **2** is lower than the pK_{a1} of many alcohols and phenols.[38] Likewise, without acid catalysis, common alcohols and phenols do not react with **1** for the same reason. Ethylation of methanesulfonic acid with **1** is rapid and nearly quantitative, because the acid pK_{a1} is much lower than that of the sulfonamide (pK_{a1} << pK_{a2}).[38]

We have carried out the catalytic ethylation of aliphatic and aryl-substituted alcohols (Equation 3) in good to excellent yields at room temperature, using tetrafluoroboric acid dimethyl ether complex (10 mol%). Preliminary small-scale reactions were easily followed by NMR spectroscopy in carbon tetrachloride or deuterochloroform; most were complete in less than 10 minutes at room temperature. In carbon tetrachloride, the byproduct sulfonamide **2** precipitated from solution as the reaction progressed. Small aliphatic alcohols including primary,

Table 2 Sulfonimidate Ethylation of Weaker Acids

Entry	Acid	pK_a	Time[a]	Product	Yield[b] (%)
1	2-Br$C_6H_4CO_2H$	2.85	5 d	2-Br$C_6H_4CO_2Et$	47
2	2-HO$C_6H_4CO_2H$	2.97	5 d	2-HO$C_6H_4CO_2Et$	60[c]
3	3,4-$Cl_2C_6H_3CO_2H$	3.71	5 d	3,4-$Cl_2C_6H_3CO_2Et$	71
4	PhCH(OH)CO_2H	3.85	2 d	PhCH(OH)CO_2Et	95[d]
5	4-Br$C_6H_4CO_2H$	3.96	5 d	4-Br$C_6H_4CO_2Et$	49
6	4-Cl$C_6H_4CO_2H$	4.01	5 d	4-Cl$C_6H_4CO_2Et$	34
7	PhCO_2H	4.29	5 d	PhCO_2Et	47

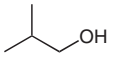
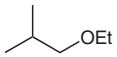
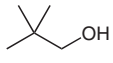
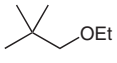
[a] In refluxing THF.
[b] Isolated yield.
[c] Crude yield.
[d] Excess acid (1.93 equiv).



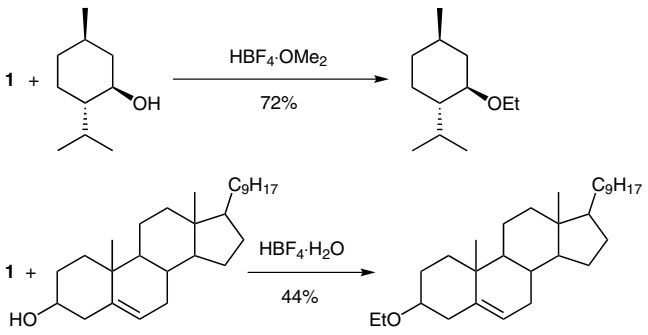
Equation 3 Sulfonimidate ethylation of alcohols

secondary, tertiary, allylic, and neopentyl were ethylated (Table 3). These volatile ethers were identified by comparison with known NMR spectra after separation from **2**. No molecular rearrangements were observed in formation of the ethyl ethers. This is particularly notable; because many of these alcohols are prone to undergo acid-catalyzed rearrangements.[10] Yields of these ethers (ranging from 78 to 94%) were calculated from NMR spectra with fluorobenzene as a quantitative, internal standard. Isolation of ethers from solid alcohols was readily accomplished on a gram scale. In the ethylation of (–)-(1*R*,2*S*,5*R*)-menthol (Scheme 5), ethyl menthyl ether was isolated in 72% yield without racemization. The optical rotation, [α] –95.6 at 20.2 °C was consistent with the literature value of [α] –89.2 at 25 °C.[39] Cholesterol was ethylated in 44% isolated yield by using 2.4 mol% of 48% aqueous fluoroboric acid as catalyst.[40]

Table 3 Sulfonimidate Ethylation of Aliphatic Alcohols Catalyzed by Fluoroboric Acid–Dimethyl Ether Complex

Entry	Alcohol	Product	Yield[a] (%)
1			81
2			80
3			79
4			94
5			78

[a] Yields were determined by NMR with an internal standard after removal of sulfonamide byproduct **2**.



Scheme 5 Sulfonimidate ethylation of menthol and cholesterol catalyzed by fluoroboric acid

Likewise, alcohols containing phenyl groups gave only single, O-ethylation products (Table 4), which were isolated by flash chromatography or Kugelrohr distillation after precipitation and filtration of **2**. These were identical to authentic ethyl ethers. Higher yields were usually obtained by Kugelrohr distillation, which is our method of choice for these liquids.

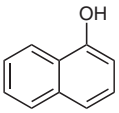
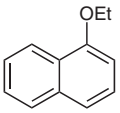
Table 4 Sulfonimidate Ethylation of Phenyl Alcohols Catalyzed by Fluoroboric Acid–Dimethyl Ether Complex

Entry	Alcohol	Time (min)	Product	Isolated yield (%)
1		<5		62[a], 62[b]
2		<15		55[a], 85[b]
3		<30		79[b]
4		<30		70[a]

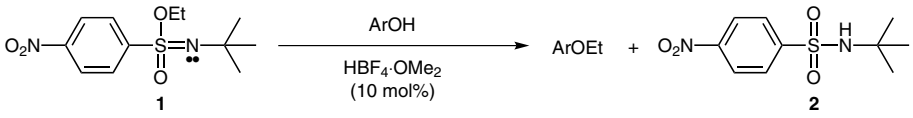
[a] Isolated by flash chromatography.
[b] Isolated by Kugelrohr distillation.

Acid-catalyzed ethylation of phenols (Equation 4) gave ethyl ethers. Catalyzed reactions proceeded faster and in higher yields for phenols with electron-donating groups compared with those having electron-withdrawing groups. This suggests that the more electron-rich phenolic oxygens are more nucleophilic in this ethylation reaction. Purification of both alcohol and phenol ethers is easily accomplished by precipitation of the sulfonamide byproduct **2** with pentane, filtration, and treatment with sodium hy-

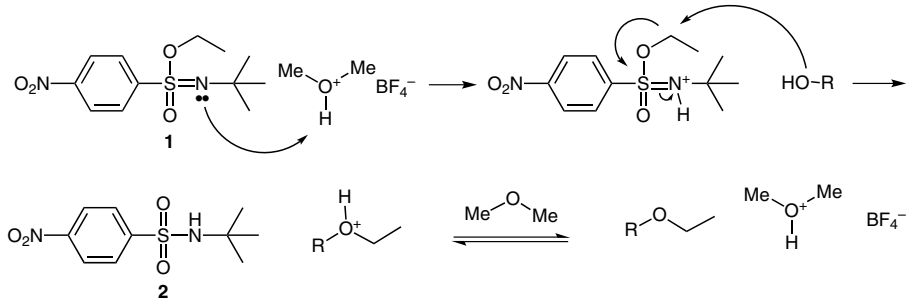
Table 5 Sulfonimidate Ethylation of Electron-Rich Phenols Catalyzed by Fluoroboric Acid–Dimethyl Ether Complex

Entry	Phenol	Time (min)	Products	Yield (%)
1	PhOH	<30	PhOEt	70[a]
2	4-MeC_6H_4OH	<30	4-MeC_6H_4OEt	87[b]
3	4-*t*-BuC_6H_4OH	90	4-*t*-BuC_6H_4OEt	59[b]
4	4-HOC_6H_4OH	<60	4-$EtOC_6H_4OEt$	45[c,d]
5	4-$EtOC_6H_4OH$	<60	4-$EtOC_6H_4OEt$	46[c]
6		<30		68[a]

[a] Isolated by flash chromatography.
[b] Isolated by Kugelrohr distillation.
[c] Crystallized solid.
[d] From 2.2 equiv of **1**.



Equation 4 Sulfonimidate ethylation of phenols



Scheme 6 Proposed mechanism for catalyzed ethylation of alcohols and phenols

dride to remove residual sulfonamide, alcohols, or phenols and any other protic substances. Final purification is accomplished by Kugelrohr distillation and/or flash chromatography to give ethers identical to authentic samples (Table 5 and Table 6).

Table 6 Sulfonimidate Ethylation of Electron-Deficient Phenols Catalyzed by Fluoroboric Acid–Dimethyl Ether Complex

Entry	Phenol	Time (min)	Products	Isolated yield (%)
1	4-BrC_6H_4OH	<50	4-BrC_6H_5OEt	54
2	C_6Cl_5OH	<60	C_6Cl_5OEt	32
3	2,4,6-$Cl_3C_6H_2OH$	<120	2,4,6-$Cl_3C_6H_2OEt$	59

Based upon analogy to alkylations by amide acetals,[2] a mechanism for the catalyzed ethylation reactions is proposed in Scheme 6. The protonated intermediate of the product ether could catalyze the next alkylation reaction by direct protonation of another sulfonimidate molecule.

A stable, crystalline 4-nitrobenzenesulfonimidate[1] can be prepared by a novel, direct O-ethylation of a sulfonamide in high yield. This reagent readily ethylates acids to esters without a catalyst, and alcohols and phenols to ethers with fluoroboric acid catalyst. The stronger the acid, the faster it alkylates and in higher yield. The more electron-rich an alcohol or phenol is, the faster it is catalytically alkylated by the sulfonimidate, and in higher yield. The sulfonimidate **1** is a *hard* alkylating agent, which prefers oxygen over nitrogen and sulfur. Alkylation reactions occur with a wide variety of labile acids, alcohols, and phenols to give products without molecular or geometric rearrangements, or racemization. Isolation of pure reaction products is easy and recycling of the byproduct sulfonamide **2** to the sulfonimidate reagent **1** is atom efficient and trivial. Therefore, sulfonimidates are excellent alternatives to diazoalkane, trialkyloxonium tetrafluoroborate, and other alkylating agents.

Results from another stable, crystalline sulfonimidate reagent with a secondary, isopropyl alkylating group will be reported soon,[1a] along with electrophilic aromatic substitutions by sulfonimidates and O-alkylations of amides.

All reactions were carried out in oven-dried glassware. CH_2Cl_2 was purified through an M Braun solvent purification system. Commercially obtained Ag_2O was finely ground, dried and stored in a darkened vacuum oven for at least an hour before use. All other commercially obtained chemicals were used as obtained, unless noted otherwise. NMR spectra were recorded on a Bruker 500, 400, or 300 MHz instrument in $CDCl_3$ or CCl_4. All of the alkylation products are common esters or ethers; many of which are commercially available and have spectra published in spectral data bases. References are given for those that are less common. Copies of spectra of the known products are provided in the Supporting Information. Melting points are uncorrected. Flash chromatography was accomplished with Redi*Sep*™ disposable columns by Isco, Inc. Mass analyses were carried out at the University of California, Riverside High Resolution Mass Spectrometry Facility, Riverside, CA, USA.

***N-tert*-Butyl-4-nitrobenzenesulfonamide (2)**

A previously filtered solution of 4-nitrobenzenesulfonyl chloride (45 g, 204 mmol) in anhydrous CH_2Cl_2 (150 mL) was added slowly (over a 1-h period) to an ice-cooled solution of *t*-$BuNH_2$ (27.9 g, 40.0 mL, 381 mmol) in anhydrous CH_2Cl_2 (150 mL). After addition, the mixture (containing white solids) was stirred overnight at r.t. The precipitate was vacuum filtered; the orange filtrate was concentrated by rotary evaporation to give the crude product as a yellow solid; crude yield: 51.31 g (98%); mp 98–105 °C; this material could be recrystallized (MeOH–H_2O, 100 mL:35 mL) to give light yellow crystals; yield: 45.71 g (87%) mp 109–111 °C (Lit.[41] 108.5–110 °C).

IR (KBr): 3274, 3107, 2989, 2877, 1612, 1538, 1358, 1172, 1091, 998, 855 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (s, 9 H), 5.23 (s, 1 H), 8.11 (d, *J* = 9.0 Hz, 2 H), 8.36 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CHCl_3$): δ = 30.1, 55.4, 124.3, 128.2, 149.2, 149.7.

Ethyl *N*-*tert*-Butyl-4-nitrobenzenesulfonimidate (1)
N-*tert*-Butyl-4-nitrobenzenesulfonamide (**2**, 5.7 g, 22 mmol) was dissolved in anhydrous CH_2Cl_2 (30 mL) in a 250-mL aluminum-foil-covered round-bottom flask with a condenser and drying tube. Commercial Ag_2O (5.11 g, 22 mmol) and molecular sieves (0.5 g) (both of which had been finely ground and heated in vacuo in the dark at 100 °C for at least 1 h) and EtI (12.3 g, 79 mmol) were added to the mixture. This was refluxed with vigorous stirring overnight [TLC (hexane–EtOAc, 3:1 + 1% Et_3N) monitoring]. Additional EtI (0.5 mL, 6.3 mmol) and anhydrous Ag_2O (1.7 g, 7.1 mmol) were added and the mixture was refluxed overnight again. If substantial sulfonamide **2** remained after 2 d, then additional EtI, Ag_2O, and molecular sieves were added and the mixture was refluxed for a further 1 d. Solids were removed by vacuum filtration with a fritted funnel and Celite or glass filter paper. The filtrate was treated with NaH (0.36 g, 15 mmol), which had been rinsed with hexane (3 ×). The mixture was stirred overnight and vacuum filtered to remove the sodium sulfonamide salt. The filtrate was concentrated by rotary evaporation to give light yellow crystals; crude yield: 6.012 g (95%); mp 51–53 °C). The yield may vary (85–95%) depending upon the dryness of the materials and the quality of the Ag_2O. Recrystallization was accomplished, if needed, by dissolving approximately one part sulfonimidate **1** in four parts MeOH (at r.t.) and cooling overnight in a freezer (mp 53–55 °C). Successive concentrating of the filtrates and cooling in a freezer afforded additional product.

IR (KBr): 3111, 2983, 1609, 1532, 1366, 1308, 1219, 1168, 1027, 906, 848, 765, 695 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7 Hz, 3 H), 1.43 (s, 9 H), 3.92 (q, *J* = 7 Hz, 2 H), 8.13, (d, *J* = 9 Hz, 2 H), 8.31 (d, *J* = 9 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.1, 33.1, 56.6, 66.3, 124.2, 129.1, 146.1, 150.1.

HRMS: *m/z* [M + H] calcd for $C_{12}H_{19}N_2O_4S$: 287.1060; found: 287.1068.

Anal. Calcd for $C_{12}H_{18}N_2O_4S$ (286.35): C, 50.33; H, 6.34; N, 9.78. Found: C, 50.79; H, 6.46; N, 9.71.

Ethylation of Strong Acids; General Procedure
The acid was added to a concentrated solution of sulfonimidate **1** (10% molar excess) dissolved in CH_2Cl_2. A mild exotherm was generally observed. Brief rotary evaporation to remove most of the solvent was followed by addition of pentane to precipitate solid byproduct **2** and residual **1**. In some cases the reaction was run in pentane or hexane. Vacuum filtration followed by rotary evaporation of the pentane filtrate produced the crude ester product. Evaluation of the expected product (whether solid or liquid) and of TLC results helped to determine whether flash chromatography and/or Kugelrohr (short path) distillation would be better for purification. Most simple esters have the highest R_f values and lowest boiling points among the residues remaining in the product, so purification is usually straightforward.

Ethyl 2,2-Dichloroacetate
Sulfonimidate **1** (0.859 g, 3.00 mmol) was dissolved in anhydrous CH_2Cl_2 (1.5 mL) and added dropwise to a 25-mL round-bottom flask containing dichloroacetic acid (250 μL, 0.375 g, 3 mmol). The solution warmed up upon addition and imparted a fruity odor characteristic of esters (TLC monitoring). Within 5 min, most of **1** appeared to have reacted and a significant amount of the byproduct sulfonamide **2** had been produced. The solution was concentrated by rotary evaporation and pentane (5 mL) was added. The pentane solution was pipetted out, leaving the undissolved sulfonamide crystals behind. A small amount of NaH (0.1 g, 4 mmol) was added to the pentane solution to precipitate salts of any unreacted acid and residual **2**. The solution was pipetted from the solids, concentrated, and purified by Kugelrohr distillation to give ethyl dichloroacetate; yield: 0.27 g (58%). IR and ^1H NMR spectra were identical to published spectra.

Ethyl Methanesulfonate
Sulfonimidate **1** (0.546 g, 1.906 mmol, 1.1 equiv), dissolved in pentane (ca. 100 mL), was treated with methanesulfonic acid (112.5 μL, 166.6 mg, 1.734 mmol) by syringe. The reaction was allowed to take place for 15 min before concentration by rotary evaporation to remove most of the pentane solvent. The liquid portion of the mixture of solid byproduct **2** and pentane solution was pipetted through a Pasteur pipet fitted with glass wool and a few centimeters of silica gel. The filtrate was collected in a 25-mL round-bottom flask. An additional few mL of pentane were used to rinse residual solids and filtered through the same pipet. The resulting solution was concentrated and purified by Kugelrohr distillation to give ethyl methanesulfonate; yield: 192 mg (89%). ^1H NMR spectra was identical to the published spectrum.

Ethyl Trifluoroacetate
Sulfonimidate **1** (30 mg, 105 μmol, 1.1 equiv), dissolved in CCl_4 (0.5 mL), was added to an NMR tube followed by TFA (7.1 μL, 10.9 mg, 95.2 μmol). The tube was shaken and analyzed by NMR to observe that the reaction was complete. The mixture was filtered through a Pasteur pipet fitted with glass wool and 2-cm of silica gel to remove the byproduct sulfonamide **2**. The filter was rinsed with additional CCl_4 (0.25 mL) into a separate NMR tube. $CDCl_3$ (0.25 mL) and a drop of TMS were added for NMR analysis. Only ethyl trifluoroacetate was observed.

Ethyl 4-Toluenesulfinate
4-Toluenesulfinic acid (0.156 g, 1.00 mmol) was dissolved in a minimal amount of CH_2Cl_2 (ca. 10 mL) and sulfonimidate **1** (0.315 g, 1.10 mmol, 1.1 equiv) was added to the solution. The mixture was stirred at r.t. for less than 50 min and then CH_2Cl_2 was removed by rotary evaporation. Pentane was added and solids were filtered. The purity of the filtrate was determined by TLC (hexane–EtOAc, 6:1). After Kugelrohr distillation and TLC analysis, the product was dissolved in pentane and treated with NaH (1 mmol) to remove protic impurities. The solids were removed by filtration and pentane was removed in vacuo to give the product; yield: 0.141 g (74%).

Ethyl 2-Bromobenzoate; Typical Procedure for Ethylation of Weaker Acids
Sulfonimidate **1** (0.859 g, 3.00 mmol) and 2-bromobenzoic acid (0.601 g, 3.00 mmol) were refluxed in THF (25 mL) for 5 d. TLC analysis (hexane–EtOAc, 6:1) showed that most of **1** had been converted into the sulfonamide **2**. The mixture was concentrated by rotary evaporation and pentane (5 mL) was added. The pentane solution was removed by pipet and treated with NaH to precipitate any unreacted acid and residual **2**. This solution was pipet filtered, concentrated in vacuo and purified by Kugelrohr distillation; yield: 0.32 g (47%). IR and ^1H NMR spectra were identical to published spectra.

Ethyl 2-Hydroxy-2-phenylacetate
Sulfonimidate **1** (0.535 g, 1.87 mmol) and *dl*-mandelic acid (0.55 g, 3.61 mmol, 1.93 equiv) were refluxed in distilled THF (10 mL) for 2 d. TLC (hexane–EtOAc, 5:1) confirmed completion of the reaction. The mixture was extracted with sat. $NaHCO_3$ until the organic layer showed no mandelic acid spot on TLC. The organic layer was dried (anhyd $MgSO_4$) and purified by flash chromatography (hexane–EtOAc, 5:1). Fractions were collected and concentrated to give the product; yield: 0.319 g (95%); mp 30–31 °C.

IR (KBr): 1733 (C=O), 3468 cm^{-1} (OH).

MS: *m/z* = 180 (base peak).

NMR-Scale Ethylation of Alcohols; General Procedure
Sulfonimidate **1** (30 mg, 0.105 mmol, 10 mol% excess) and alcohol (0.97 mmol) were dissolved in CCl_4 (0.5 mL) along with an internal quantitative standard of PhF (2.3 μL, 0.024 mmol, 25 mol% of al-

cohol) and added to an NMR tube. The alcohols studied were 2-methylpropan-1-ol, butan-2-ol, 2-methylpropan-2-ol, but-3-en-2-ol, and neopentyl alcohol. Spectra of each mixture were run before addition of HBF_4·OMe_2 (1.0 μL, 9.7 μmol, 10 mol% of the alcohol amount). The NMR tubes were capped and inverted several times before recording the progress of each reaction. Reactions were followed by observing the disappearance of the sulfonimidate **1** *tert*-butyl peak at δ = 1.38 (in CCl_4) and the appearance of the sulfonamide **2** *tert*-butyl peak at δ = 1.23. In each spectrum, a small singlet appeared at δ = 3.2, which corresponds to Me_2O from the catalyst. Reactions with aliphatic alcohols were complete in less than 15 min. Several molecular sieve pellets were added to each NMR tube to neutralize the catalyst after completion of the reaction. Each product was isolated, by pipetting the CCl_4 solution from the precipitated sulfonamide **2**. The samples were squeezed with a large pipet bulb through a cotton-plugged Pasteur pipet containing silica gel (ca. 3 cm). Each was rinsed with additional CCl_4 (2 × 0.25 mL) into an NMR tube for analysis. Excellent yields of the ethyl ethers of each alcohol were observed. No evidence for molecular rearrangements was seen.

(1*R*,2*S*,5*R*)-2-Ethoxy-1-isopropyl-4-methylcyclohexane
(–)-(1*R*,2*S*,5*R*)-Menthol (1.000 g, 6.40 mmol, mp 42.5–43.7 °C) and sulfonimidate **1** (2.017 g, 7.04 mmol) were dissolved in magnetically stirred, anhydrous CCl_4 (20 mL) in a septum-capped 50-mL round bottom flask with a drying tube. HBF_4·OMe_2 (66 μL, 0.64 mmol) was added [TLC (hexane–EtOAc, 4:1 + 1% Et_3N) monitoring]. After 4.5 h, the mixture was flash chromatographed (silica gel, 5 cm, 1-cm diameter column) to kill the catalyst and remove the sulfonamide byproduct **2**. The reaction flask was rinsed with pentane (3 × 5 mL) and flushed through the column. Solvent was removed by rotary evaporation, followed by evacuation under high vacuum to give the product; yield: 0.846 g (72%). The average optical rotation for the product (three determinations) was $[\alpha]_D$ –95.6 at 20.2 °C. The structure was confirmed by ^{1}H NMR (400 MHz) and GC/MS.

(3β)-3-Ethoxycholest-5-ene
Sulfonimidate **1** (1.254 g, 4.38 mmol) and cholesterol (1.226 g, 3.17 mmol) were dissolved in anhydrous CH_2Cl_2 (10 mL) and treated with 48% aq HBF_4 catalyst (10.0 μL, 2.4 mol%) [TLC (hexane–EtOAc, 4:1 + 1% Et_3N) monitoring; aluminum-backed silica gel plates were developed after elution by dipping in an acid developer (5% H_2SO_4, 45% (95%) EtOH, and 50% anisaldehyde by volume) with heating until blue cholesterol spots appeared against a peach background]. The reaction was complete after 1 h, when the sulfonimidate and cholesterol spots disappeared. At that point, a few mg of molecular sieves were added to the mixture to neutralize the acid. After rotary evaporation, hexane (30 mL) was added to the concentrate and the mixture was stirred overnight. Solids were vacuum filtered to give a clear filtrate, which was chromatographed (silica gel, hexane–Et_2O, 1:4). Clear fractions were concentrated by rotary evaporation to give a white solid; yield: 0.573 g (44%); that was recrystallized (EtOH). The mixed melting point with commercial (Sigma) product was not depressed (88–88.5 °C). ^{1}H NMR spectrum of the synthetic product was identical to that of cholesteryl ethyl ether. Sulfonamide **2** was obtained (0.768 g, 68%) from the reaction.

3-Ethoxypropylbenzene; Typical Procedure
Sulfonimidate **1** (1030 mg, 3.60 mmol) and 3-phenylpropan-1-ol (409 mg, 3.0 mmol) were dissolved in pentane (ca. 8 mL). The clear, yellow solution was magnetically stirred for at least 5 min before HBF_4·OMe_2 catalyst (31 μL, 0.30 mmol) was added. Bubbling occurred immediately and a white precipitate was observed. The flask was warm to the touch. The reaction was complete in <30 min, as observed by precipitation of **2**, then left to stand overnight. The next day, the precipitate appeared to be tan. The precipitate was filtered by vacuum and rinsed with pentane. The filtrate was concentrated by rotary evaporation to obtain the crude product. Kugelrohr distillation gave pure product; yield: 389 mg (79%).

1-*tert*-Butyl-4-ethoxybenzene; Typical Procedure for Reactions with Electron-Rich Phenols
Sulfonimidate **1** (1.030 g, 3.60 mmol) and 4-*tert*-butylphenol (0.450 g, 3.00 mmol) were dissolved in pentane (10 mL). The mixture was magnetically stirred for at least 5 min before HBF_4·OMe_2 (31 μL, 0.3 mmol) was added. A light pink precipitate was observed within 5 s. After 90 min the reaction was complete, but TLC still showed the presence of the phenol. After placing the plate in the I_2 chamber, 2 new spots were observed. The new spots were assumed to be derivatives of the phenols, possibly due to electrophilic aromatic substitution. After stirring overnight and filtering the precipitate, TLC showed that multiple spots were still present. As a result, rinsed NaH (171 mg, 4.41 mmol) suspended in pentane was added with an eyedropper to react with the phenols. Bubbling occurred and the tan-colored solution was stirred for ca. 10 min. The mixture was allowed to settle for ca. 30 min. TLC showed multiple spots. Another same amount of NaH was added and less bubbling occurred. The mixture was left to sit overnight. The following day, TLC showed only two faint spots rather than four or five. Sodium alkoxide salt was then filtered out with a fritted funnel and the filtrate was transferred into a tared 25-mL round-bottom flask. The filtrate was concentrated by rotary evaporation and Kugelrohr distilled to obtain a pure product; yield: 0.313 g (59%).

1-Bromo-4-ethoxybenzene; Typical Procedure for Reactions with Electron-Deficient Phenols
Sulfonimidate **1** (299 mg, 1.04 mmol) and 4-bromophenol (129 mg, 0.746 mmol) were added to a magnetically stirred round-bottom flask fitted with a septum. Anhydrous CH_2Cl_2 (ca. 2 mL) was added, followed by HBF_4·OMe_2 catalyst (7.7 μL, 10 mol% of the amount of phenol) [TLC (hexane–EtOAc, 4:1 + 1% Et_3N) monitoring]. After 50 min, when the reaction was complete (loss of TLC spot for **1**), the catalyst was quenched with several dry molecular sieve pellets. Molecular sieves were filtered and rinsed with CH_2Cl_2, and the filtrate was concentrated by rotary evaporation. The concentrate was dissolved in anhydrous CH_2Cl_2 (1 mL) and loaded onto a flash chromatography column (silica gel, 5 g, hexane); yield: 81 mg (54%).

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are copies of ^{1}H and ^{13}C NMR spectra of compounds **1** and **2** and of ^{1}H spectra of ethylation products reported in this study.

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