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Process Research on the Preparation of 1-(3-Trimethylsilylphenyl)-2,2,2-trifluoroethanone by a Friedel–Crafts acylation Reaction

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Abstract:

Zifrosilone (1-(3-trimethylsilylphenyl)-2,2,2-trifluoroethanone) (3) is a cholinesterase inhibitor that has been studied for the treatment of Alzheimer's disease. Process research has been carried out on a route to convert phenyltrimethylsilane to 3 by Friedel–Crafts acylation using trifluoroacetic anhydride. Kinetics and products analyses suggest that the optimal conditions for this reaction are noncatalytic amounts of aluminum chloride, dichloromethane solvent and as low a temperature as can be practically used in a scaled-up process. Significant separation challenges to isolate 3 from the isomer byproduct 1-(4-trimethylsilylphenyl)-2,2,2-trifluoroethanone) (4) remain. These challenges were investigated using vapor–liquid equilibrium studies.

1. Introduction

Zifrosilone (1-(3-trimethylsilylphenyl)-2,2,2-trifluoroethanone) (**3**) is a cholinesterase inhibitor that has been studied for the treatment of Alzheimer's disease.[1–8] The preferred synthetic method has been a bis-metalation process, starting with 1,3-dibromobenzene and sequentially attaching the trimethylsilyl and trifluoroacetyl groups, to form **3**.[9,10] A warning regarding the potential explosiveness of 3-bromophenyllithium, a potential byproduct in this and some other potential routes to Zifrosilone, should be noted.[11] An earlier version of the present research was reported in a U.S. Patent application.[12]

The aluminum chloride catalyzed electrophilic aromatic substitution (trifluoroacylation−deprotonation) of arenes by trifluoroacetic anhydride (TFAA) has recently been cited in the literature.[13–16] However, the reaction of such trimethylsilyl arenes as phenyltrimethylsilane (**1**) and 1,3-bis(trimethylsilyl)benzene[17–22] (**2**) with TFAA is not so clear-cut (Scheme 2). The trimethylsilyl group has been known to be displaced from aromatic rings by acyllium ions. Thus, **2** has been reacted with acetyl chloride and aluminum chloride in carbon disulfide solvent to form 3-trimethylsilyl acetophenone in a yield of 44%.[23] Another paper cites this reaction (with acetic anhydride) as occurring with "excellent yields".[24]

Ipso substitution of **2** has been reported with dichloromethylmethyl ether and aluminum chloride (in dichloromethane solvent) to form, after workup with water, trimethylsilyl benzaldehydes (Scheme 1).[25] The regiochemistry for the reaction, however, was only 89% *meta* product, with 9.5% of *p*-trimethylsilylbenzaldehyde also formed. Compound **2** has been reacted with (hydroxy(tosyloxy)iodo)benzene in acetonitrile solvent to effect an *ipso* electrophilic aromatic substitution

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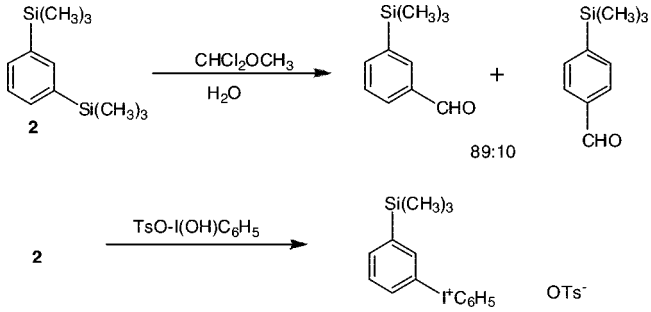
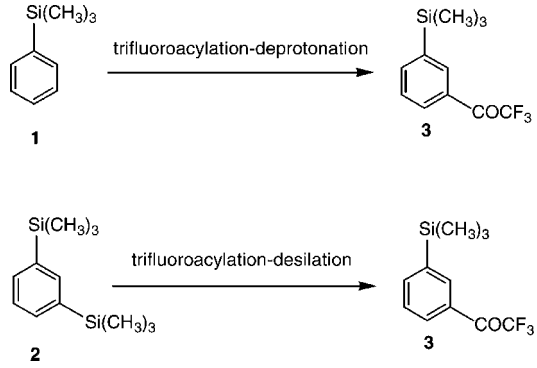
Scheme 1. ***ipso*** **substitutions of compound 2 with dichloromethylmethyl ether[25] and with hydroxy(tosyloxy)iodobenzene (Koser's reagent)[26]**



Scheme 2. **Potential pathways from phenyltrimetnylsilane or 1,3-bis(trimethylsilyl)benzene to 1-(3-trialkylsilylphenyl)-2,2,2-trifluoroethanone**



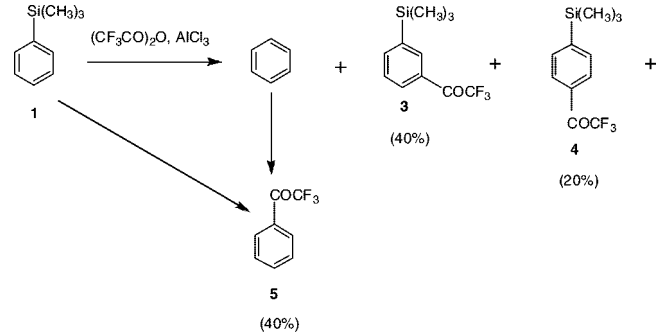
(Scheme 1).[26] A 24% isolated yield of (3-trimethylsilyl)phenyl, phenyl iodonium tosylate (the *ipso* substitution product) was obtained. Electrophilic *ipso* substitutions of aryltrimethylsilanes have been reviewed.[27] Before the present study was initiated, it was unclear whether the target product **3** could be made by the Friedel–Crafts acylation of **1** by trifluoroacetic anhydride in an economically competitive process.

2. Results and Discussion

At the beginning of this study, the expected starting material to prepare **3** was to be either phenyltrimethylsilane (**1**) or 1,3-bis(trimethylsily1)benzene (**2**) (see Scheme 2). The amounts of products and byproducts observed under the most favorable reaction conditions for the conversion of **1** to **3** are given in Scheme 3. The amounts of products and byproducts observed under the most favorable reaction conditions for the conversion of **2** to **3** are given in Scheme 4. Throughout this publication the yields cited are solution yields by gas chromatography analyses.

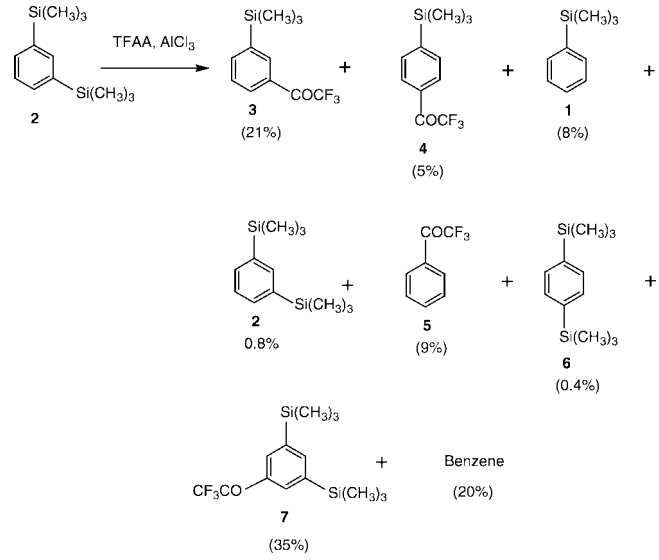
Conversion of 1 to 3 via Friedel–Crafts acylation. The results for 14 experimental trials for the reaction of **1** with TFAA, using aluminum chloride as Friedel–Crafts catalyst, are given in Table 1. The trimethylsilyl group is known to act like a proton as far as directing electrophilic aromatic substitution, with Hammett σ values for the TMS group for both *meta* and

Scheme 3. **Reaction of trimethylsilylbenzene with trifluoroacetic anhydride[a]**



[a] Compound **5** could be formed directly from **1** by *ipso* substitution or via benzene intermediate by protonation−desilation of **1**, followed by trifluoroacylation–deprotonation. Compounds **3** and **4** can be formed from **1** by direct trifluoroacylation−deprotonation.

Scheme 4. **Reaction of 1,3-bis(trimethylsilyl)benzene with trifluoroacetic anhydride**



para substitution close to zero.[28] This would explain the nearly 2 to 1 isomer ratio of *meta* to *para* substitution (twice as much **3** formed as **4**). Because of the large size of the trimethylsilyl group, one would not have expected any substitution *ortho* to the TMS group.

Comparison of Methylene Chloride and Cyclohexane Solvents. A comparison of conversion of phenyltrimethylsilane to products and byproducts of this study is made in Table 1 for the solvents dichloromethane and cyclohexane. The reactions to form **3** and **4** in cyclohexane went through an induction period, which could be a real practical concern upon scale up. This induction period was not observed in dichloromethane solvent. The reaction in cyclohexane required a 15–20° higher temperature, as compared to the reaction in dichloromethane. The conversion of **1** to **3** was somewhat higher in dichloromethane, and the reaction seemed cleaner, as compared to the reaction in cyclohexane. However, relatively less **4** byproduct was made in cyclohexane solvent. In cyclohexane solvent the product molar ratios of **3** to **4** were 2.4:1 (see entries 4, 6,

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Table 1. **Experimental trials for the reaction of phenyltrimethylsilane with trifluoroacetic anhydride (reactions carried to completion)[a]**

			mol/mol		mol fraction of starting **1**[b]					
entry	solvent[c]	*T*, °C	TFAA/**1**	$AlCl_3$/TFAA	PhH	**1**	**3**	**4**	**5**	$ArCF_3$[d]
1	CH_2Cl_2	−10	1.10	1.00	0.39	0.16	0.20	0.10	0.15	0.45
2	CH_2Cl_2	−11	1.10	2.73	0.39	n.d.	0.21	0.10	0.30	0.61
3	CH_2Cl_2	−12	0.33	0.97	0.16	0.68	0.09	0.04	0.03	0.16
4	C_6H_{12}	−10	0.40	2.00	0.27	0.36	0.18	0.08	0.11	0.37
5	CH_2Cl_2	−10	0.50	2.00	0.43	0.06	0.24	0.12	0.14	0.50
6	C_6H_{12}	8	0.50	2.00	0.35	0.47	0.09	0.04	0.05	0.18
7	C_6H_{12}	2	0.50	2.00	0.23	0.27	0.22	0.09	0.19	0.50
8	CH_2Cl_2	−18	0.50	2.00	0.41	0.11	0.22	0.11	0.15	0.48
9	CH_2Cl_2	−18	1.00	2.00	0.42	0.00	0.23	0.11	0.24	0.58
10[e]	CH_2Cl_2	−34	0.50	2.00	0.33	0.37	0.18	0.09	0.04	0.31
11[e]	CH_2Cl_2	−34	0.50	2.00	0.29	0.43	0.16	0.08	0.05	0.29
12	C_7H_{14}	2	0.50	1.94	0.60	0.24	0.07	0.03	0.05	0.15
13	CH_2Cl_2	−18	1.50	1.33	0.43	0.01	0.22	0.11	0.24	0.57
14	CH_2Cl_2	22	1.00	1.00[f]	0.45	0.00	0.13	0.07	0.32	0.52
15	TFAA	23	5.32	0.38	0.12	0.47	0.03	0.01	0.36	0.40

[a] Analyses of products solutions were done on a Hewlett-Packard Series II 5890 gas chromatograph, using a silica column. [b] With dichloromethane solvent, up to 4% benzene converted was to diphenylmethane, and less than 1% of benzene was converted to (*m*-trifluoroacetyl)phenyltrimethylsiloxyldimethylsilane and 3-benzyl-trifluoroacetophenone. With cyclohexane solvent, up to 4% of benzene was converted to dimethyldiphenylsilane, up to 4% of benzene was converted to phenylpentamethyldisiloxane, and less than 1% of benzene was converted to diphenyltetramethyldisiloxane. The numbers in this table have been normalized not to include these silicon-derived related products. [c] Dichloromethane (CH_2Cl_2), cyclohexane (C_6H_{12}) or methylcyclohexane (C_7H_{14}). [d] Total of trifluoroacetylated aromatics. [e] Entries 10 and 11 were experiments run under the same conditions (repeat experiments). These reactions were not run to completion. [f] Also contained $FeCl_3$ at initial molar ratio 1.00 versus TFAA.

and 7, Table 1). The reaction in cyclohexane seemed to have a very narrow temperature range within which to operate the reaction. Below 0° the reaction was too slow, and above 10° the reaction gave lower yields of **3**.

Reaction Condition Variables for Trifluoroacylation Route to Form Compound 3. Experiments are summarized in Table 1. Mol fractions of products and byproducts from late aliquots are given in the right six columns of Table 1. The following conclusions may be suggested:

(1) Increasing the initial molar ratio of $AlCl_3$ to TFAA from 1.0 to 2.7 did not affect significantly the conversion of **1** to **3** or **4** (compare entries 1 and 2). The main effect of this increase was to convert more of **1** to benzene and to **5**. When a molar excess of aluminum chloride to TFAA was used, the yield of **3** and **4** was nearly independent of the initial molar ratio of TFAA to **1** for dichloromethane solvent (compare entries 8, 9, and 13).

(2) If less than 50 mol % of TFAA (versus **1**) was used, less **3** and **4** were formed (compare entries 3, 4, and 5, Table 1). Increasing the initial molar ratio of TFAA to **1** above 0.5 did not increase the conversion of **1** to **3**.

(3) A series of experiments using methylene chloride were done at three temperatures, −10 (entry 5), −18 (entry 8), and −34 °C (entries 10 and 11). On the basis of conversion of **1**, these results suggest that lower temperatures were advantageous for the reactions to form **3** and **4** in dichloromethane solvent.

(4) The use of methylcyclohexane as solvent seemed to accelerate the protiodesilation side reaction, as compared to using cyclohexane solvent (compare entries 6 and 12). The reaction in methylcyclohexane was very complicated, resulting in many new unassigned peaks detected by gas chromatography.

(5) An attempt to use TFAA as the solvent (run 40) resulted in a low yield of **3** (compare entries 14 and 15).

Screening of Potential Catalysts for the Conversion of Phenyltrimethylsilane to Compound 3. Several other Lewis acid type catalysts were tried in order to determine if they gave higher yields of **3**. In all of these tests, the reaction conditions were 20 °C, with initial 1:1 molar ratio of TFAA:**1** and with dichloromethane or cyclohexane as solvents. The catalyst trials fell into two groups. Ferric chloride, boron trifluoride diethyl etherate, stannic chloride and titanium tetrachloride gave essentially no reaction (almost quantitative reactant **1** recovered). Ferric bromide, polyphosphoric acid, boron trichloride and trifluoromethane sulfonic acid gave almost total conversion of **1** to benzene. None of these agents catalyzed the formation of either **3** or **4** in amounts greater than 1%.

Conversion of 2 to 3 via Protiodesilation/Friedel–Crafts acylation and/or Trifluoroacyldesilation (*ipso*) Substitution. By analogy to the reported *ipso* acyldesilation by acetyl chloride[23] and acetic anhydride,[24] the reaction of trifluoroacetic anhydride with **2**, in the presence of aluminum chloride, was expected to give **3**. When this reaction was tried, the major product was the trisubstituted 3,5-bis(trimethylsilyl)trifluoroacetophenone (**7**, see Scheme 4). This product would result from a normal Friedel–Crafts reaction. Related products **1** and benzene could be explained by protiodesilation reactions on **2**. These related products could in turn be reacted in the normal Friedel–Crafts mechanism to form **5** (from benzene) and **3/4** (both from **1**). Some additional **3** (but not **4**) might have been formed by protiodesilation of **7**. The results of the aluminum chloride catalyzed reactions of trifluoroacetic anhydride and reactant **1** in dichloromethane (see Table 1) support the combination of protiodesilation and normal Friedel–Crafts trifluoroacyldeprotonation as major reaction pathways from reactant **2**.

Another, less likely, possibility is that competing *ispo* trifluoroacyldesilation reactions occurred to form **5** (directly from **1**) and **3** (directly from **2**). If the *ipso* reaction were the only mechanism, one would have expected a final molar ratio of **3** to **4** of 20:1.[29] If the combined protiodesilation/trifluoroacyl-

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Table 2. **Rate constants determined using SimuSolv software fitting of kinetic data of entries 8 and 9 of Table 1**

rate constant	at −18 °C (× 10^5)	at −34 °C (× 10^5)	units	E_a (J/mol)	ln A	k_{xy} calcd at −47 °C (× 10^5)
k_{13} (**1** → **3**)	4.75	0.999	s^{-1}	46.7	12.0	0.262
k_{14} (**1** → **4**)	2.23	0.501	s^{-1}	44.8	10.3	0.137
k_{1B} (**1** → PhH)	10.42	1.83	s^{-1}	52.2	15.3	0.401
k_{B5} (PhH → **5**)	18.83	1.67	M^{-1} s^{-1}	72.6	23.2	0.021

deprotonation were the only mechanism, one would have expected a final molar ratio of **3** to **4** of 2:1, unless some **3** forms from **7**. Since the experimental molar ratio of **3** to **4** from **2** was 4.08, one could estimate that 79% of the trimethylsilyltrifluoroacetophenone products come from the protiodesilation/trifluoroacyldeprotonation reaction pair, and 21% of these products come from the direct *ipso* reaction on **2**. An estimation of the competition between the protiodesilation and trifluoroacyldesilation (*ipso*) reactions might be made by comparing the amounts of protiodesilation products (benzene and phenyltrimethylsilane plus 79% of trifluoroacetophenone and 79% of the trimethylsilyltrifluoroacetophenone products) to the possible *ipso* products (21% of **5** and 21% of the trimethylsilyltrifluoroacetophenone products). This estimation predicts a 12% contribution of *ipso* reaction, in the competitive reaction pathways from reactant **2**.

Kinetics Experiments in Dichloromethane Solvent. The highest solution yields of the desired product **3**, based on reactant **1**, were around 23–24%, in dichloromethane solvent (Table 1). These yields are slightly less than but still comparable to the yields of **3** from 1,3-dibromobenzene via the bis-metalation routes.[9,10] Kinetic analyses were done on the trifluoroacylation of **1**, using SimuSolv software, for two of the higher yield reactions for **3**, entry 8 (run at −18 °C) and entry 10 (done at −34 °C; see Table 1). The following reactions were analyzed using the numerical integration methods of SimuSolv software. This software optimizes the fit of calculated rate constants to the experimental amounts of reactant and products by the method of maximum likelihood function.[30] The convention of the rate constants is to signify the reactants and products. Thus, k_{13} refers to the rate constant for the reaction of **1** going to product **3**. The following kinetic expressions were proposed in order to determine the value of the rate constants for experiments 8 and 10:

$$-d(\mathbf{1})/dt = k_{13}(\mathbf{1}) + k_{14}(\mathbf{1}) + k_{1B}(\mathbf{1})$$

where B refers to the byproduct benzene

$$d(\mathbf{3})/dt = k_{13}(\mathbf{1})$$

$$d(\mathbf{4})/dt = k_{14}(\mathbf{1})$$

$$d(B)/dt = k_{1B}(\mathbf{1}) - k_{B5}(B)(TFAA)$$

$$d(\mathbf{5})/dt = k_{B5}(B)(TFAA)$$

In the kinetic expressions above, k_{13}, k_{14} and k_{1B} are first-order rate constants. Rate constant k_{B5} is second-order. The results obtained from the SimuSolv software-fitting of the kinetic data of runs 8 and 10 are given in Table 2. The plots of experimental data versus fitted curves for runs 8 and 10 are given in Figure 1.

The best fits for the experimental data versus calculated rate constants were made for the model above, in which the unit processes to convert **1** to **3**, **4** and benzene are all first-order overall (first order in **1**). The kinetic model predicts that the unit process to convert benzene to **5** is second order overall (first order in benzene and first order in trifluoroacetic anhydride). It is important to emphasize that just because the best curve fitting was obtained using these assumptions, this does not prove the unit processes or mechanisms for the formation of **3**, **4** and **5**. Therefore, one should not speculate, in the absence of more experimental results, about the possible differences in mechanisms for the trifluoroacylation of **1** versus the trifluoroacylation of benzene, based solely on these curve fitting estimations. As discussed earlier, one cannot rule out the simultaneous competition of an *ipso* substitution pathway from **1** to make **5**.

Given these caveats, one can make some speculations regarding the possible "optimal" conditions to run a potential process to convert **1** to **3**, by using TFAA/$A1C1_3$ in dichloromethane solvent. The calculations summarized in Table 3 suggest that lower temperatures for the reaction would enhance the formation of **3** and **4** slightly, as compared to the protiodesilation reaction to form benzene. However, the trifluoroacylation of benzene would be more significantly retarded at lower temperatures, since this unit process has the largest Arrhenius activation energy, by 20 J/mol. The larger preexponential factor for the protiodesilation reaction of **1** to form benzene, as compared to the trifluoroacyldeprotonation reactions to form **3** and **4**, suggests less steric crowding at the highest energy transition state for the protiodesilation process.

The activation parameters calculated and shown in Table 2 were used to calculate rate constants for the four unit processes at −47 °C, which are given in column seven of Table 2. Using four sets of rate constants at four temperatures, one can estimate final yields of **3** and the three related products. The results of these calculations at −34 and −47 °C are given in Table 3.

These calculations suggest that the optimal temperatures to operate the proposed process to make **3** might be as low as −47 °C. The yield of **3** from **1** would maximize at around 32%. The formation of **4** and benzene would still be significant side reactions. However, at −47 °C, the trifluoroacylation of benzene would be predicted to occur so slowly that related product **5** would be formed at less than 1%. This depressed side reaction would free up more trifluoroacetic anhydride to be used in the desired reaction to form **3**. However, a serious downside to running the reaction at −47 °C would be the predicted long time for the reaction to go to completion (around 150 h).

Other Related Products from the Friedel–Crafts Trifluoroacylation of 1. Attempts were made to identify any related products formed in the proposed trifluoroacylation process in dichloromethane or cyclohexane solvents. The identification of these other related products were done by gas chromatography/mass spectrometry (Table 4). The accountabilities of starting **1** for the reactions at larger scales for the two solvent systems were excellent. This suggests that most all of the related products in the two experiments have been identified.

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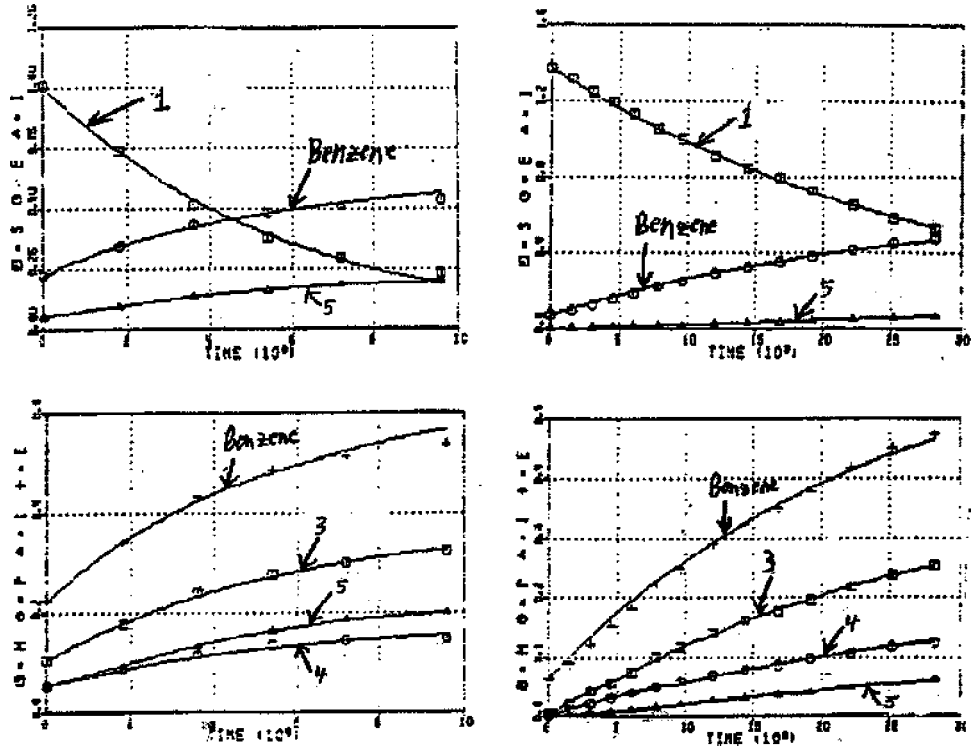

Figure 1. **SimuSolv software curve fittings of experimental kinetics data from experiments 8 and 10. Run 8, dichloromethane at −18 °C; run 10, dichloromethane at −34 °C.**

Table 3. **Experimental and calculated (using rate constants of Table 2) amounts of product and byproducts (mol % from 1) for TFAA acylation of phenyltrimethylsilane at several temperatures**

	at −10 °C	at −18 °C	at −34 °C	at −47 °C
reaction hours	6.0	7.0	30	150
expt or calcd	expt	expt	calcd	calcd
3	23.8	22.2	27.9	32.2
4	11.6	10.7	14.0	16.9
1	6.3	10.5	2.6	1.3
PhH	43.7	40.8	47.2	49.**1**
5	14.1	15.4	8.4	0.4

Table 4. **Gas chromatographic and mass spectroscopic identification of major products and byproducts from reaction of TFAA and phenyltrimethylsilane in dichloromethane and cyclohexane solvents**

		MS ion peaks (g/mol)			
compound	GC retention time (min)	parent	largest	second largest	third largest
5	3.5[a]	174	105	77	51
3	6.8[a]	246	231	232	91
4	7.3[a]	246	231	232	134
$C_{13}H_{19}O_2F_3Si_2$[b]	9.6[a]	320	255	305	151
diphenylmethane	11.1[a]	168	168	167	165
3-Bn-TFA[c]	15.2[a]	264	195	264	165
3	23.6[d]	246	231	232	91
$C_{11}H_{20}OSi_2$[e]	23.8[d]	224	209	210	97
4	24.8[d]	246	231	232	134
DMDPS[f]	36.2[d]	212	197	212	198
$C_{16}H_{22}OSi_2$[g]	39.6[d]	286	271	193	28

[a] Dichloromethane solvent. GC Conditions: start at 90 °C (0 time hold), ramp 8 °C/min to 180 °C, then 10 min hold. [b] (*m*-Trifluoroacetyl)phenyltrimethylsiloxyldimethylsilane. [c] 3-Benzyl-trifluoroacetophenone. [d] Cyclohexane solvent. GC Conditions: start at 70 °C (15 min hold), ramp 5 °C/min to 240 °C, then 0 time hold. [e] Phenylpentamethyldisoxlane. [f] Dimethyldiphenylsilane. [g] Diphenyltetramethyldisiloxane.

Analyses of Distillation Fractions from the Larger-Scale Preparations of 2. If the trifluoroacylation route from **1** to **3** were done in a commercial process, a crucial part of the process would be the successful isolation of the final product by some separation process, such as distillation or preparative chromatography. Such a separation would be dependent on the relative volatility differences between **3**, **4** and the other related products produced in the reaction. Compounds **3** and **4** were removed easily from the higher boiling related products produced in the proposed trifluoroacylation process by flash distillation. These higher boilers would include diphenyldimethylsilane and diphenyltetramethyldisiloxide (from the reaction in cyclohexane) and diphenylmethane and two other related products (from the reaction in dichloromethane). A low-boiling related product (phenylpentamethyldisiloxane) would also be separated readily from **3** and **4**.

The results of a flash vacuum distillation of the product isolated from experiment 5 (largest scale trial) are given in Table 5. The relative volatilities of components of various distillation cuts from two experiments are given in Table 6. The volatility of **5** is about 10 times higher than that of **3**, and **5** was separated easily as a forecut in the distillation of **3**. Product **3** is 30−60% more volatile than its isomer **4**. Early fractions (3–5) have greater than a 2:1 ratio of **3** versus **4** (Table 5). Assuming a relative volatility of **3** to **4** of 1.60, it is estimated that a separation of the two isomers, to obtain 99.9% pure **3**, would require a 36-stage distillation column.[31,32]

(31) The author thanks K. A. Cobb, L. S. Green, R. Srivastava and P. Au-Yeung of the Department of Analytical Sciences of The Dow Chemical Company for the Vapor-Liquid Equilibrium measurements of the compounds of this study.

Table 5. **Flash distillation fractions of products from experiment 5 (by GC analyses)**

fraction	weight (g)	(8 torr) temp (°C)	molar fractions[a] 5	3	4	DPM[b]
1	4.61	22–47	0.979	0.015	0.005	0.001
2	6.10	47–74	0.911	0.066	0.022	0.002
3	7.12	74–85	0.086	0.681	0.217	0.016
4	6.04	85	0.006	0.722	0.252	0.020
5	8.67	85–87	0.004	0.687	0.283	0.026
6	6.46	87	0.001	0.636	0.330	0.034
7	6.86	87–89	n.d.	0.538	0.398	0.049
8	3.71	89–104	n.d.	0.310	0.488	0.159
9	0.89	104–117	n.d.	0.071	0.326	0.519
pot	7.07	undistilled	n.d.	n.d.	0.003	0.669

[a] Molar fractions of starting compound **1**. [b] Diphenylmethane.

Table 6. **Relative volatilities of product 3 versus related products from Friedel–Crafts trifluoroacylation of 1, measured from distillation fractions from reactions 4 and 5 (expressed as volatility of product 3 over volatility of related product)**

fraction	**3/4** (mol/mol) in fraction	relative volatilities at 130 °C (**3**/*X*) **4**	**5**	DPM[a]	$C_{11}H_{20}OSi_2$[b]	DMDPS[c]
2	3.0[d]	1.66	0.05	n.d.	n.d.	n.d.
3	3.1[d]	1.60	0.09	10.9	n.d.	n.d.
4	2.9[d]	1.59	0.10	10.1	n.d.	n.d.
5	2.4[d]	1.58	0.10	10.8	n.d.	n.d.
6	1.9[d]	1.61	0.12	11.2	n.d.	n.d.
7	1.4[d]	1.60	n.d.	12.4	n.d.	n.d.
8	0.6[d]	1.57	n.d.	12.5	n.d.	n.d.
av[e]		1.60	0.09	11.3		
av[f]		1.57	0.09	17.9		
1	3.2[g]	1.29	n.d.	n.d.	0.77	12.8
2	2.6[g]	1.24	n.d.	n.d.	0.58	29.2
av[h]		1.26			0.68	21.0
av[i]		1.20			0.58	

[a] Diphenylmethane. [b] Phenylpentamethyldisoxlane. [c] Dimethyldiphenylsilane. [d] From reaction in dichloromethane solvent. [e] Average from seven fractions measured at 130 °C. [f] Average from seven fractions measured at 80 °C. [g] From reaction in cyclohexane solvent. [h] Average from two fractions measured at 130 °C. [i] Average from two fractions measured at 80 °C.

3. Conclusions

The Friedel–Crafts trifluoroacylation of phenyltrimethylsilane is a potential route to make Zifrosilone. The advantages to this process versus the existing bis-metalation process from 1,3-dibromobenzene are that the Friedel–Crafts process would be only one step from readily available phenyltrimethylsilane, and that the reactants, intermediates and products are relatively less hazardous. The overall yields of **3** from the two processes are comparable. The disadvantage of the proposed Friedel–Crafts process is the relatively large amount of **4**, the isomer to **3**, which would necessitate a challenging purification of **3** by distillation or chromatography. Vapor–liquid equilibria and kinetics studies of the proposed Friedel–Crafts process enabled an analysis of the challenges raised in the present study. Because Zifrosilone was never manufactured at Dowpharma, the final choice between the existing two-step process and the one-step process of the present study was never made.

(32) P. Au-Yeung, The Dow Chemical Company, personal communication, based on VLE results in Table 6.

4. Experimental Section

Gas chromatograms were obtained with a Hewlett-Packard Series II 5890 gas chromatograph. Gas chromatograms/mass spectra were done with a Hewlett-Packard Series II 5890 gas chromatograph, connected to a Hewlett-Packard 5971 Series mass selective detector, with Series 59822E ionization gauge controller. Nuclear magnetic resonance spectra (H^1 and C^{13}) were taken on a Bruker AC 300 spectrophotometer. NMR spectra of some of the compounds of this study are given in Supporting Information.

Largest Scale Friedel–Crafts Trifluoroacetylation of Phenyltrimethylsilane (1); Experiment 5, Table 1. A reaction flask containing aluminum chloride (66.67 g, 500 mmol) and 185 mL of chloromethane was cooled to −10 °C, and trifluoroacetic anhydride (52.50 g, 250 mmol) was added to the contents, in 5 min. The temperature of the reaction slurry increased to +5 °C. After the slurry had cooled again to −10 °C, neat phenyltrimethylsilane (75.00 g, 500 mmol) was added, over a 10 min period. The temperature of the resulting slurry rose to −3 °C and then fell back to −10 °C after 40–45 min. This suggests the presence of an exothermic reaction.[33]

The reaction slurry was stirred at −10 °C for 370 min, and nine aliquots were taken during this time to be analyzed by GC. At the end of the reaction, the brown reaction solution was decanted away from remaining solids into a suitable flask, and the reaction flask was rinsed with 100 mL of fresh dichloromethane. The organic material was poured into a stirred and chilled mixture of 400 g of ice/water, in such a way as to allow the temperature of the resulting mixture to reach only 13 °C. A dichloromethane rinse (75 mL) of the flask originally containing the organic material was also added to the cold organic/aqueous slurry. The organic phase (cloudy and yellow) was separated from the acidic aqueous phase. The organic phase was stirred three times with 450 mL of cold fresh water. The pH readings of the aqueous phases after the washes were successively 1.5, 2.8 and 3.8. The resulting dichloromethane layer was dried with anhydrous magnesium sulfate. The dried dichloromethane layer was isolated by filtration, and the solvent was removed by evaporation under vacuum. Volatiles were stripped at a final vacuum of 20 torr at 13 °C. A dark orange-brown oil remained (59.3 g). The organic material after evaporation was distilled under vacuum, with most of the distillation at 8 torr. Nine distillation fractions were collected and analyzed by GC (Table 5). The combined weights of the fractions and distillation pot residue were 57.5 g (97.0% material balance).

NMR Spectra of Reactants, Related Product and Crude Product. Reactant **1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.49 (m, 2H), 7.32–7.30 (m, 3H), 0.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.6, 133.5, 129.0, 127.0, −0.70. Related product **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 2H), 7.69–7.51 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 130.2, 129.2. Crude product mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15–8.05 (m, 6.5H), 7.50–7.03 (m, 22H), 4.11–4.00 (m, 8.4H), 0.20/0.16/

(33) A group additivity thermal calculation, using CHETAH software created by The Dow Chemical Company, estimated that the conversion of **1** to **3** released 46 J/mol of energy. The author thanks J. Downey, Department of Analytical Sciences, The Dow Chemical Company for this calculation.

0.09 (3xs, total 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 139.5, 130.6, 130.2, 129.8, 129.6, 129.4, 129.25, 129.19, 128.8, 128.6, 128.3, 127.6, 126.9, 116.7, 115.0, 42.1, 1.7, 1.3, 0.1.

Relative Volatilities of Reaction Products. Vapor–liquid equilibria were measured for the various products and related products for these two reactions, using distillation fractions from experiments 4 and 5.[31] These results are summarized in Table 6.

Small-Scale Trials of Friedel–Crafts Trifluoroacetylation of Phenyltrimethylsilane (1). Many variations on the experimental conditions to prepare **3** via a Friedel–Crafts process using aluminum chloride catalyst were tried. These reactions were done at the 10–70 mmol (for reactant **1**) scale. Reaction variables such as solvent, concentration, temperature, molar ratios of reactants and time of reaction were studied. The results of these studies are given in Table 1.

Attempted *ipso* Substitution of 1,3-Bis(trimethylsilyl)benzene To Prepare 3. A flask containing aluminum chloride (2.00 g, 15 mmol) and 30 mL of dichloromethane was cooled below −10 °C. A solution of trifluoroacetic anhydride (1.10 g, 5.5 mmol) in 10 mL of dichloromethane was added to the reaction flask, and the resulting slurry was cooled again to −10 °C. A solution of **2** (1.16 g, 4.8 mmol) in 10 mL of dichloromethane was added in 1 min to the stirred and chilled reaction slurry.

The reaction was run at −12 °C for 500 min, with a total of 16 aliquots removed to be analyzed by gas chromatography. The composition in molar fractions of the last aliquot (at 500 min reaction time) was the following: Benzene (0.199), **1** (0.082), **2** (0.008), **3** (0.211), **4** (0.052), **5** (0.094), **6** (0.004) and **7** (0.350).

Supporting Information Available

Additional chromatographic and NMR information. This material is available free of charge via the Internet at http://pubs.acs.org.

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