# Reaction Pathway for the Formation of 3,3-Diphenyl-1-benzenesulfonamidopropane in the Aluminum Chloride Catalyst Reaction of 1-Benzenesulfonyl-2-(bromomethyl)ethylenimine and Benzene

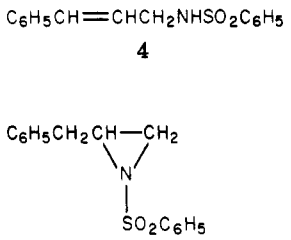
Walter J. Gensler* and Surendra K. Dheer

*Department of Chemistry, Boston University, Boston, Massachusetts 02215*

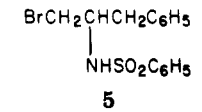
*Received March 9, 1981*

The Friedel–Crafts reaction of 1-benzenesulfonyl-2-(bromomethyl)ethylenimine-2-$^{14}C$ and benzene yields 3,3-diphenyl-1-benzenesulfonamidopropane-2-$^{14}C$. This finding, coupled with the results of an earlier tracer study, shows that the order of atoms in the three-carbon chain of the starting ethylenimine persists unchanged in the product. If so, a previously suggested pathway becomes unacceptable. Of the several test compounds exposed to the action of aluminum chloride and benzene as described in the present work, only 1-benzenesulfonyl-2-benzylethylenimine and 1-benzenesulfonyl-2-phenylazetidine gave 3,3-diphenyl-1-benzenesulfonamidopropane. Since the azetidine compound could be eliminated as an intermediate in the ethylenimine process, this left only the benzyl derivative as an eligible intermediate. These data led to a revised pathway, which accommodates all the facts. An early stage in the mechanism is taken as conversion of the ethylenimine starting material to 1-benzenesulfonyl-2-benzylethylenimine. Under the reaction conditions, the latter compound generates a carbocationoid center on the middle carbon atom of its three-carbon chain. By a 1,2 hydride shift, this carbocation rearranges to the more stable benzylic carbocation, which combines with benzene to form the final product.

1-Benzenesulfonyl-2-(bromomethyl)ethylenimine (1) reacts with benzene in the presence of aluminum chloride (see Scheme I). to yield 3,3-diphenyl-1-benzenesulfonamidopropane (3).[1] A carbon-14 labeling experiment showed that the 3-carbon atom of the starting ethylenimine 1 emerges as the 1-position of the product, as in 3.[2] A test of the compounds 1-benzenesulfonyl-2-phenylazetidine (2), *N*-cinnamylbenzenesulfonamide (4), 1-bromo-3-phenyl-2-



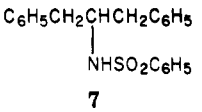
4



5



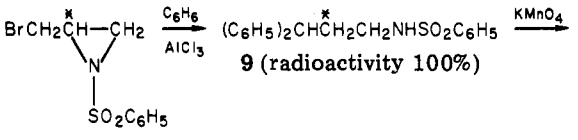
6



7

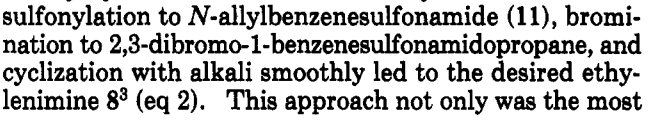
benzenesulfonamidopropane (5), 1-benzenesulfonyl-2-benzylethylenimine (6), and 1,3-diphenyl-2-benzenesulfonamidopropane (7) as possible intermediates showed that, under the conditions of the Friedel–Crafts reaction, only azetidine 2 gave 3,3-diphenyl-1-benzenesulfonamidopropane.[2] On the basis of these facts, a reaction pathway, formulated as in 1 → 3,[1,2] was proposed.

To gain further insight into the Friedel–Crafts conversion, we have now carried out another tracer experiment, this time with the ethylenimine 2-carbon atom labeled as in 8. Reaction pathway 1 → 3 predicts that the carbon



8

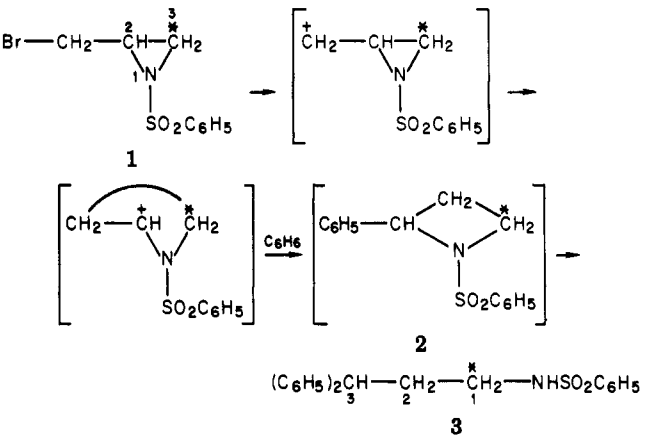
9 (radioactivity 100%)



10 (radioactivity 0.6%) (1)

at position 2 of the starting ethylenimine 8 will appear at position 3 of the 3,3-diphenyl-1-benzenesulfonamidopropane product. But this requirement was not met. Oxidative degradation of the 3,3-diphenyl product 9 produced benzophenone 10 free of radioactivity. Therefore, position 3 of the Friedel–Crafts product must also be free of activity. This new piece of evidence made sequence 1 → 3 untenable and led us to reexamine the course of the reaction. The present paper reports the new work and presents a revised reaction path.

Scheme I

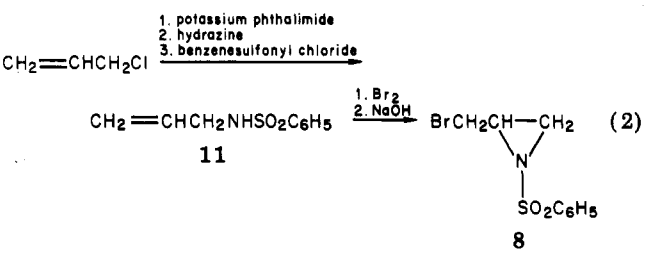


1

2

3

**Preparation and Reaction of 1-Benzenesulfonyl-2-(bromomethyl)ethylenimine-2-$^{14}C$ (8).** Three routes for the synthesis of labeled material 8 were explored. Pilot runs showed that allyl chloride could be converted efficiently by the Gabriel method to allylamine. Benzenesulfonylation to *N*-allylbenzenesulfonamide (11), bromination to 2,3-dibromo-1-benzenesulfonamidopropane, and cyclization with alkali smoothly led to the desired ethylenimine 8[3] (eq 2). This approach not only was the most



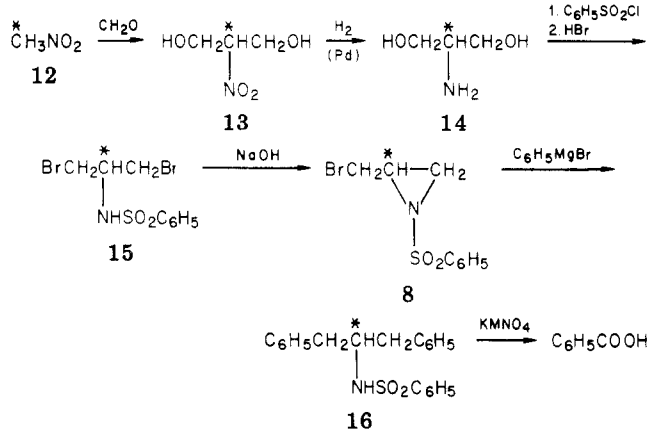
11

8 (2)

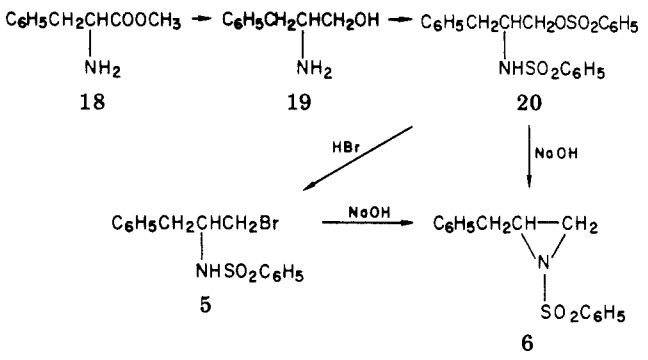
(1) Gensler, W. J.; Rockett, J. C. *J. Am. Chem. Soc.* **1955**, *77*, 3262.
(2) Gensler, W. J.; Koehler, W. R. *J. Org. Chem.* **1962**, *27*, 2754.

0022-3263/81/1946-4051$01.25/0 

Scheme II



Scheme III



straightforward,[4,5] but it gave the highest overall yield (34%); we would have used it were it not for the cost of allyl-2-$^{14}C$ chloride. Another synthesis started with diethyl malonate, which we planned to label on its central carbon. In cold runs, the malonate was nitrosated, and the nitroso product was reduced with lithium aluminum hydride to 1,3-dihydroxy-2-aminopropane. Several additional steps led to 1-benzenesulfonyl-2-(bromomethyl)ethylenimine. The relatively poor overall yield made this preparation unattractive.

The synthesis that was finally adopted started with nitromethane-$^{14}C$ (**12**), available from labeled methyl iodide.[6] Condensation with formaldehyde converted the nitromethane to 1,3-dihydroxy-2-nitropropane (**13**),[7] which on catalytic hydrogenation gave 1,3-dihydroxy-2-aminopropane (**14**, Scheme II). The derived 1,3-bis(benzenesulfonyloxy)-2-benzenesulfonamidopropane reacted with hydrogen bromide to yield 1,3-dibromo-2-benzenesulfonamidopropane (**15**). Exposure to alkali cyclized compound **15** smoothly to 1-benzenesulfonyl-2-(bromomethyl)-ethylenimine-2-$^{14}C$ (**8**). For confirmation of the location of the label, the ethylenimine **8** was converted by reaction with phenylmagnesium bromide to 1,3-diphenyl-2-benzenesulfonamidopropane-2-$^{14}C$ (**16**). This was oxidized to benzoic acid, which proved to be free of activity. The label, accordingly, was fixed at the central carbon. The overall yield of radioactive 1-benzenesulfonyl-2-(bromomethyl)ethylenimine-2-$^{14}C$ (**8**) by this sequence was 18%.

As indicated above, the key Friedel–Crafts reaction with benzene and labeled ethylenimine **8** yielded radioactive 3,3-diphenyl-1-benzenesulfonamidopropane (**9**) devoid of activity at its 3-position. Since the ethylenimine 2-position supplies none of the carbon at the propane 3-position (cf. **8** to **9**) and since we have established before that the ethylenimine 3-position is the precursor for the propane 1-position, this leaves only the ethylenimine 2-position as the source of for the 2-position of 3,3-diphenyl-1-benzenesulfonamidopropane. Taken together, these findings establish the fact that the chain of three carbon atoms in 1-benzenesulfonyl 2-(bromomethyl)ethylenimine persists intact in the propane spine of the Friedel–Crafts product. Whatever the mechanism, it cannot involve breaking the carbon to carbon bonds. Since the **1** to **3** reaction pathway does precisely this, it is unacceptable.

**Preparation and Testing of Possible Intermediates in the Friedel–Crafts Reaction of 1-Benzenesulfonyl-2-(bromomethyl)ethylenimine with Benzene.** At this point we resorted to the devise of exposing benzene solutions of various compounds that conceivably might be involved as intermediates to the action of aluminum chloride. If 3,3-diphenyl-1-benzenesulfonamideopropane failed to form, any pathway that led through the compound being tested could be excluded. If 3,3-diphenyl-1-benzenesulfonamideopropane were obtained, the test compound would become eligible for consideration as a possible intermediate.

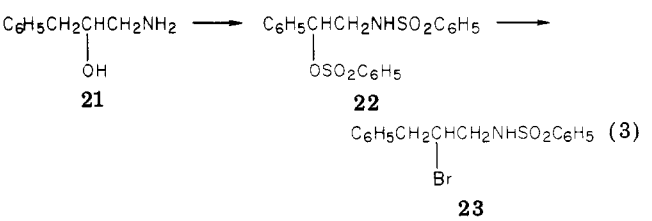
The candidate test compounds, listed in Table I, were synthesized as follows. *N*-(3-Bromoallyl)benzenesulfonamide (**17**),[5] *N*-cinnamylbenzenesulfonamide (**4**),[1] 1-

$$\underset{\mathbf{17}}{BrCH{=}CHCH_2NHSO_2C_6H_5}$$

bromo-3-phenyl-2-benzenesulfonamidopropane (**5**),[8] and 1,3-diphenyl-2-benzenesulfonamidopropane (**7**)[1] were prepared essentially by following directions worked out before.

1-Benzenesulfonyl-2-benzylethylenimine (**6**) was obtained by reducing the methyl ester **18** of phenylalanine to 3-phenyl-2-amino-1-hydroxypropane **19** (Scheme III), attaching benzenesulfonyl groups to both oxygen and nitrogen and cyclizing with alkali to the desired candidate material **6**. Converting the bis(benzenesulfonyl) derivative **20** to a 1-bromo-3-phenyl-2-benzenesulfonamidopropane (**5**) before cyclization to **9**[8] offered little advantage.

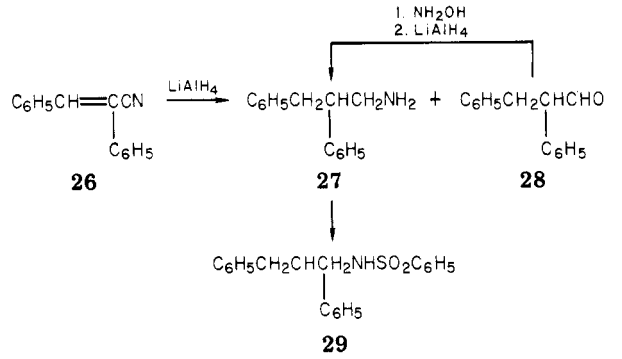
1-Phenyl-2-bromo-3-benzenesulfonamidopropane (**23**) was the product obtained by displacing the benzenesulfonate group in 1-phenyl-2-(benzenesulfonyloxy)-3-benzenesulfonamidopropane (**22**) with bromide (eq 3).



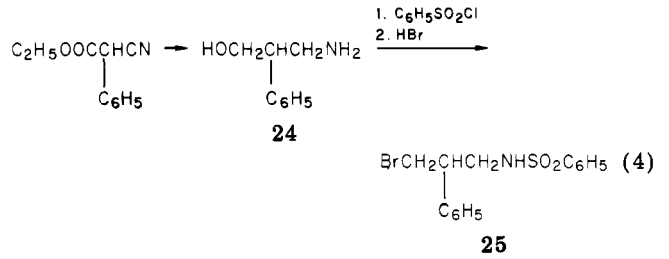
The bis(benzenesulfonyl) precursor **22** came from 1-phenyl-2-hydroxy-3-aminopropane (**21**), which was conveniently accessible by adding ammonia to benzylethylene oxide.[9]

(3) Gensler, W. J. *J. Am. Chem. Soc.* **1948**, *70*, 1843.
(4) A further improvement would start by allylating the sodio derivative of *N*-(ethoxycarbonyl)benzenesulfonamide with allyl chloride[5] and continuing by bromination and finally treatment with alkali.
(5) Gensler, W. J.; Frank, F. J.; Dheer, S. K.; Lauher, J. W. *J. Org. Chem.* **1971**, *36*, 4102.
(6) Cf.: Arnstein, H. R. V.; Bentley, R. *J. Chem. Soc.* **1951**, 2385.
(7) The method is an improved adapation of the directions described before. Cf. ref 3 as well as: Schmidt, E.; Wilkendorff, R. *Chem. Ber.* **1919**, *52*, 389.
(8) Gensler, W. J.; Rockett, J. C. *J. Am. Chem. Soc.*, **1952**, *74*, 4451.
(9) Fourneau, E.; Trefouel, Mme. *Bull. Soc. Chim. Fr.* **1928**, *43* (4), 454.

Scheme IV




Reducing ethyl phenylcyanoacetate furnished 3-hydroxy-2-phenyl-1-aminopropane (**24**) isomeric with amino alcohol **21** (eq 4). Dibenzenesulfonation followed by




treatment with hydrobromic acid led to 3-bromo-2-phenyl-1-benzenesulfonamidopropane (**25**), isomeric with **23**.

Another possible intermediate, 1,2-diphenyl-3-benzenesulfonamidopropane (**29**, Scheme IV), was obtained from the corresponding amine **27**, which in turn was available as the reduction product from 2-phenylcinnamonitrile (**26**). To obtain additional amounts of amine **27**, we converted the 2,3-diphenylpropanal (**28**), also obtained from the reduction process, to its oxime and reduced it further.

Table I summarizes the results of testing the candidate compounds as intermediates in the Friedel–Crafts reaction. In every case we followed a standardized set of directions whereby a benzene solution of 1-benzenesulfonyl-2-(bromomethyl)ethylenimine and aluminum chloride in the molar ratio of 1:1.5 was refluxed for a set period. Different conditions made comparisons of yields, equivocal, since the results depended on the parameters. There was evidence, for example, that the molar ratio of substrate to catalysis affected the yield. Also, control experiments established that 3,3-diphenyl-1-benzenesulfonamidopropane gradually decomposed when it was kept under the conditions of its formation.

Table I shows that only 1-benzenesulfonyl-2-phenylazetidine (**2**) and 1-benzenesulfonyl-2-benzylethylenimine (**6**) are eligible for consideration as mainline intermediates in the conversion of 1-benzenesulfonyl-2-(bromomethyl)-ethylenimine to 3,3-diphenyl-1-benzenesulfonamidopropane. These two are the only test compounds that give the 3,3-diphenyl product in yields greater than the 20–30% obtained from 1-benzenesulfonyl-2-(bromomethyl)-ethylenimine itself. Although other test compounds (**4**, **23**, **25**) gave the product, the low yields were not convincing. Interestingly, 2,3-diphenyl-1-benzenesulfonamidopropane (**29**) was isolated together with the 3,3-diphenyl isomer from test compound **23**, as well as from **25**, and, as seen from the first entry in Table I, even from 1-benzenesulfonyl-2-(bromomethyl)ethylenimine (**1**). *N*-(3-Bromoallyl)benzenesulfonamide (**17**) gave benzenesulfonamide as the only recognized product. 3-Phenyl-1-bromo-2-benzenesulfonamidopropane (**5**), 1,3-diphenyl-2-benzenesulfonamidopropane (**7**), and 2,3-diphenyl-1-benzenesulfonamidopropane (**29**) were recovered unchanged.

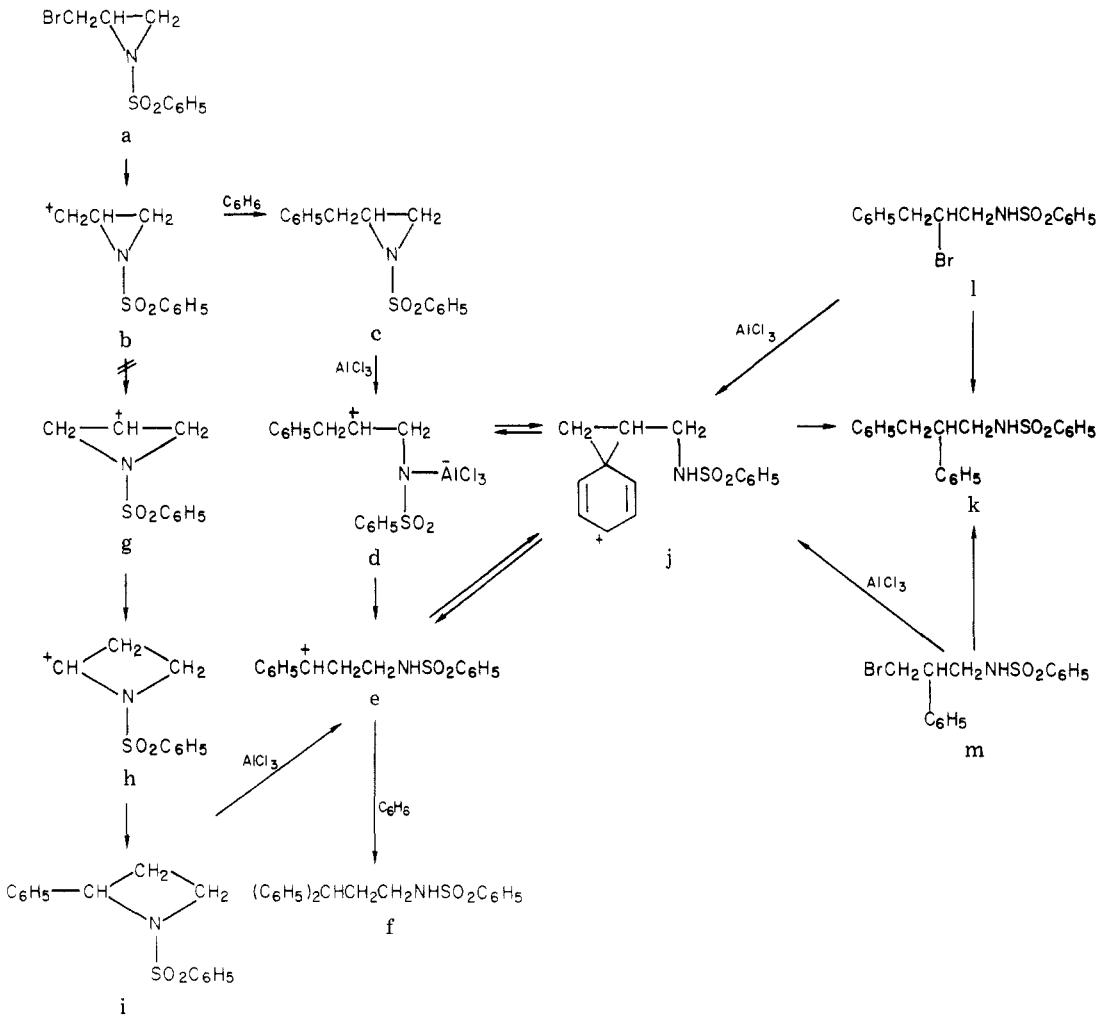
The fact that we isolated significant amounts of product from 1-benzenesulfonyl-2-benzylethylenimine (**6**) clashed with the result observed before,[1] which was that compound **6** gave only intractable tars. But the earlier finding was clearly in error, a consequence very likely of the difficulty in separating individual compounds from the crude Frie-

Table I. Test of Possible Imtermediates in the Friedel-Crafts Formation of 3,3-Diphenyl-1-benzenesulfonamidopropane (3) from Ethyleneimine 1[a]

| reactant | amounts: reactant, g (mmol) | $AlCl_3$, g | $C_6H_6$, mL | % yield of 3 |
|---|---|---|---|---|
| 1[b] | 9.0 (31) | 6.5 | 128 | 15[c] |
| 17[d] | 1.8 (6.6) | 1.3 | 26 | *e* |
| 6 | 2.0 (7.2) | 1.5 | 29 | 44 |
| 2[f] | 3.5 (13) | 2.6 | 50 | 73[f] |
| 4 | 3.0 (11) | 2.2 | 43 | 1.8 ± 1.1[g] |
| 23 | 2.0 (7.2) | 1.13 | 22 | 6.5[h] |
| 25 | 2.4 (8.7) | 1.36 | 27 | 6.3[i] |
| 5 | 1.8 (6.5) | 1.0 | 20 | 0.0[j] |
| 7 | 2.0 (7.2) | 1.1 | 22 | 0.0[k] |
| 29 | 0.52 (1.9) | 0.29 | 5.8 | 0.0[l] |

[a] See the Experimental Section for details. [b] Unlabeled material. [c] After the product was removed, the crude products remaining in the combined mother liquors were chromatographed through a column of silica gel with petroleum ether (bp 30–60 °C) first and then benzene as developing solvents. Processing the various fractions furnished more of the 3,3-diphenyl-1-benzenesulfonamidopropane (3) as well as 0.67 g (7%) of 2,3-diphenyl-1-benzenesulfonamidopropane (**29**), identified by mixture melting point and by infrared and nuclear magnetic resonance comparisons. [d] See ref 5. [e] The only identified product was benzenesulfonamide (mp 149–151 °C) isolated in 46% yield. Thin-layer chromatography of the crude product revealed no trace of 3,3-diphenyl-1-benzenesulfonamidopropane. [f] See ref 2. [g] This percentage yield was obtained with the help of pure 3,3-diphenyl-1-benzenesulfonamidopropane-2-$^{14}C$ (**9**) by an isotope dilution assay. Only benzene sulfonamide was obtained in the earlier work (see ref 1). [h] After the 3,3-diphenyl product was removed, and the remaining material in the mother liquors was isolated and crystallized twice from methanol. The still slightly impure 2,3-diphenyl-1-benzenesulfonamidopropane (**29**; 0.4 g; mp 81–90 °C) so obtained was crystallized once more to give 0.18 g (9%) of pure material (mp 92–95 °C) identified by mixture melting point and by infrared and NMR comparisons. [i] Processing the ethyl alcohol mother liquors as in footnote *h* afforded 0.2 g (8%) of 2,3-diphenyl-1-benzenesulfonamidopropane (**29**), identified by melting point, mixture melting point, and its NMR absorption spectrum. [j] One crystallization of the crude product from alcohol yielded unchanged starting material **5**: 1.4 g (81%); mp 22–23 °C. Thin-layer chromatography either before or after crystallization developed only one spot. An earlier trial led to 75% recovery of starting material **5** (cf. ref 1). [k] Crystallization of the crude product from 95% alcohol gave only unchanged 1,3-diphenyl-2-benzenesulfonamidopropane (**7**), mp 107–108 °C. The recovery was 50%. Thin-layer chromatography on the crudes revealed the presence of a second component, which was not identified. The earlier trials with this starting material **7** also returned the unchanged reactant (72%; see ref 1). [l] Even with the starting reaction mixture saturated with dry hydrogen bromide, only the unchanged 2,3-diphenyl-1-benzenesulfonamidopropane (**29**) was recovered (62%). Examining the crude product by thin-layer chromatography gave no sign of 3,3-diphenyl-1-benzenesulfonamidopropane or of benzenesulfonamide.

Scheme V. Reaction Pathway for Formation of 3,3-Diphenyl-1-benzenesulfonamidopropane



del–Crafts product mixture. Recognizing benzyl derivative 6 as an eligible intermediate opens the way to consideration of a different reaction sequence, which is summarized as a → f in Scheme V.

The first step is taken as the generation of carbocation b and alkylation of benzene to form 1-benzenesulfonyl-2-benzylethylenimine (c). This process is analogous to the many cyclcopropylcarbinyl cation reactions in which the cyclopropylcarbinyl grouping is preserved in the product.[10] Next, under the influence of aluminum chloride the ring in c opens to give carbocation d which by hydride shift forms the more stable benzylic ion e. This serves as the immediate precursor of the final product, 3,3-diphenyl-1-benzenesulfonamidopropane (f). Note how the **a → f** sequence, by maintaining the integrity of the three-carbon chain, satisfies the demands of the tracer experiments.[11]

The first-formed carbocation b could conceivably rearrange by migration of nitrogen with its pair of electrons to give carbocation g. A hydride shift would product h, which could continue via azetidine i to cation e and further to the final product f. However, the b to g rearrangement, inherently disfavored because the electron-poor sulfonamido group would have to migrate, is precluded because of the symmetry of carbocation g. If g were involved as an intermediate, final product f would emerge with its propane 1- and 3-positions scrambled, contrary to fact. Accordingly, although azetidine i gives rise to 3,3-diphenyl-1-benzenesulfonamidopropane (f), this process is independent of the reaction from 1-benzenesulfonyl-2-(bromomethyl)ethylenimine (a).

The reactions in Scheme V include the possibility of the sidetracking of carbocations d and (or) e to form phenonium ion j. This provides a reasonable way (j to k) to account for formation of the 2,3-diphenyl isomer k together with the 3,3-diphenyl product f in the reaction from a. The pair of isomers l and m also yielded a mixture of the 2,3- and 3,3-diphenyl products (k and f). Phenonium ions j, as a common intermediate, presents an economical way of accounting for these results.

In summary, the formulations in Scheme V can accommodate all the facts available for the Friedel–Crafts alkylation of benzene with 1-benzenesulfonyl-2-(bromomethyl)ethylenimine to give 3,3-diphenyl-1-benzenesulfonamidopropane.

## Experimental Section

**General Methods.** All the nuclear magnetic resonance work was done with the help of a Varian 60-MHz spectrometer. Chemical shifts are given in $\delta$ values and $J$ values in hertz. Gas–liquid chromatographic analyses were obtained from an F&M instrument (Model 700) or a Research Specialty unit (B-600). Volatile solvents were removed routinely by distillation at 10–15 mm from a rotating flash held in a bath of warm water. Analyses for elements were reported by the Scandinavian Micro-Analytical

(10) Cf.: Ohal, G. A.; Schleyer, P. v. R., Eds. "Carbonium Ions"; Vol. 3, Wiley-Interscience: New York, 1972; Vol. 3 See especially chapter 25 by H. G. Richey, Jr., and chapter 26 by K. N. Wiberg, B. Andes Hess, Jr., and A. J. Ashe III.

(11) The conversion of 1,2-dichloropropane to 1,1-diphenylpropane on treatment with benzene in the presence of aluminum chloride has some resemblance to the ethylenimine process. See: Ransley, D. L. *J. Org. Chem.* **1966**, *31*, 3595.

Laboratory, Spang Micro-Analytical Laboratory, and Galbraith Laboratories. Commercially available silica gel plates from Gelman Co. (type SG) and from Eastman Co. (Type K 301 R, with and without fluorescing material) were relied on for thin-layer chromatograms.

Radioactivity measurements were made by liquid scintillation counting in a Packard Tri-Carb liquid scintillation spectrometer (Model 3002). The efficiency of the counter was determined routinely as the time measurements were being taken, with benzoic acid-$^{14}C$ as an internal standard.

**Nitromethane-$^{14}C$ (12).**[6] With transfers accomplished in a vacuum line, a total of 6.1 g (43 mmol) of radioactive methyl iodide was brought into reaction with 12 g (78 mmol) of silver nitrite in the presence of 13.4 g (220 mmol) of nitromethane. The temperature of the reaction mixture climbed slowly to 60 °C, after which the mixture was kept at reflux. The total reaction period was 2 h. After purification, the nitromethane product, showing one peak on gas–liquid chromatography, weighed 15.6 g (ca. 84% from the methyl iodide used). Since nitromethane is an effective quenching agent in liquid scintillation counting, its radioactivity was not determined.

**1,3-Dihydroxy-2-nitropropane (13).**[3,7] A solution of nitromethane-$^{14}C$ (13.1 g, 215 mmol), paraformaldehyde (19.3 g, 644 mmol), and 33% aqueous potassium hydroxide (4 drops) in 160 mL of methanol was refluxed for 30 min. The reaction mixture was brought to room temperature and filtered directly into an ice-cold solution of sodium methoxide from 7.1 g (310 mmol) of sodium and 85 mL of methanol. The precipitated solid 1,3-dihydroxy-2-nitropropane was collected, was dried (38.5 g) and then, as a suspension in ether (300 mL), was neutralized with salicylic acid (29.7 g). The isolated 1,3-dihydroxy-2-nitropropane-$^{14}C$ (13, 14.4 g) was further crystallized from ethyl acetate–chloroform and then diluted with pure nonradioactive carrier to give the final product (12.7 g), with $(1.65 \pm 0.07) \times 10^9$ dpm/mol.

**Oxalic Acid Salt of 1,3-Dihydroxy-2-aminopropane-2-$^{14}C$ (14).**[3,7] 1,3-Dihydroxy-2-nitropropane-2-$^{14}C$ (12.7g, 105 mmol; $1.65 \times 10^9$ dpm) in 150 mL of water containing 6.5 g (72 mmol) of oxalic acid was shaken in the presence of 15 g of 5% palladium-on-barium sulfate under hydrogen (51 lb/in.$^2$) for 53.5 h. Filtration gave a clear solution, which was concentrated and then flooded with acetone. The precipitated oxalate salt, dried for 16 h at 31 °C ($10^{-3}$ mm), furnished 13.8 g (96%) of the desired product, mp 200–202 °C (lit.[3,7] 200–202 °C), with $(1.7 \pm 0.09) \times 10^9$ dpm/mol of amine.

**1,3-Bis(benzenesulfonyloxy)-2-benzenesulfonamidopropane-2-$^{14}C$.** Over a period of 1 h, benzenesulfonyl chloride (0.15 mol) was added to a stirred mixture of oxalate (13.6 g, 0.098 mol) and pyridine (160 mL). The temperature was kept at 0 °C during the addition and for 1 h thereafter. The reaction mixture was then stirred at room temperature for 3 h.

Ice-cold concentrated sulfuric acid was added slowly with stirring, and the acidified mixture was extracted with chloroform. After the chloroform extract had been rinsed with portions of water, aqueous bicarbonate, and water, it was dried and then stripped of solvent. The crude, solid *O,O,N*-tribenzenesulfonyl) derivative of 14 was recrystallized from methanol to give 24 g (65–71% yields) of pure material (mp 125.5–127.5 °C) with $(1.71 \pm 0.04) \times 10^9$ dpm/mol.

**1-Benzenesulfonyl-2-(bromomethyl)ethylenimine-2-$^{14}C$ (8).** Stirring and refluxing a solution of the *O,O,N*-tribenzenesulfonyl derivative (24.9 g, 48.7 mmol) in 95% alcohol (900 mL) plus 48% hydrobromic acid (276 mL) for 2 h replaced the terminal benzenesulfonyloxy groups with bromo groups, as in 15. Without isolation of product and with the temperature held at 0 °C, 10% aqueous sodium hydroxide solution (957 mL) was introduced, after which stirring was continued for 0.5 h while the temperature was allowed to rise to room temperature. The white precipitate was collected, dried, and recrystallized several times from methanol–water and from 95% ethyl alcohol to give 1-benzenesulfonyl-2-(bromomethyl)ethylenimine-2-$^{14}C$ (8; 4.5 g, 48%; mp 86.5–87 °C) with $(1.65 \pm 0.05) \times 10^9$ dpm/mol. The product was homogeneous according to TLC on a Gelman type SG plate ($R_f$ 0.87 with benzene).

**1,3-Diphenyl-2-benzenesulfonamidopropane-2-$^{14}C$ (16).** A mixture of phenylmagnesium bromide in tetrahydrofuran, prepared from bromobenzene (4.0 mL, 38 mmol) and magnesium (1.3 g, 53 mmol), with 3.0 g (9.0 mmol) of 1-benzenesulfonyl-2-(bromomethyl)ethylenimine-2-$^{14}C$ showing $(5.49 \pm 0.17) \times 10^8$ dpm/mol plus a total of 205 mL of tetrahydrofuran that had been distilled from lithium aluminum hydride was refluxed for 72 h. After acidification with 6 N sulfuric acid, the aqueous layer was extracted thoroughly with ether, and the combined organic layers were washed in succession with portions of 10% sodium hydroxide solution, several times with water, with 4 N sulfuric acid, with saturated sodium bicarbonate solution, and finally with water. The dried organic solution was stripped of solvent, and the residual yellow solid was recrystallized from 95% ethyl alcohol to give 2.6 g (67%) of pure product, mp 106.5–108 °C (lit.[1] mp 107.5–108 °C). This material, 1,3-diphenyl-2-benzenesulfonamidopropane-2-$^{14}C$ (16), was homogeneous according to thin-layer chromatography ($R_f$ 0.79 with benzene) and did not depress the melting point of authentic material. It was radioactive to an extent of $(5.44 \pm 0.08) \times 10^8$ dpm/mol.

When phenyllithium was used instead of phenylmagnesium bromide, the only materials isolated were benzenesulfonamide (11%), phenylacetone (15%), and unchanged starting material (29%).

**Benzoic Acid by Oxidation of 1,3-Diphenyl-2-benzenesulfonamidopropane-2-$^{14}C$ (16).** A mixture of the radioactive derivative 16 (1.0 g, 3 mmol, showing $5.44 \times 10^8$ dpm/mol), potassium permanganate (5.1 g, 30 mmol), and sodium hydroxide (1.3 g) in water (155 mL) plus pyridine (10 mL) was refluxed for 3 h. The reaction mixture was cooled to 0 °C, was acidified with 25 mL of concentrated hydrochloric acid, and then was treated with saturated sodium bicarbonate solution (20 mL). The mixture, still acidic, was extracted thoroughly with ether. The combined ether layers were extracted with several portions of 1% sodium hydroxide and then water. These alkaline extracts were combined, concentrated to ca. 60 mL and then at 0 °C were acidified by adding 25 mL of cold concentrated hydrochloric acid. The precipitated benzoic acid was desiccated for 16 h at room temperature. The benzoic acid so obtained (0.86 g; mp 110–115 °C) was crystallized twice from water to give crystals: 0.29 g (46%); mp 120–121 °C. The retained radioactivity, determined to be $(5.56 \pm 0.30) \times 10^6$ dpm/mol, corresponded to $1 \pm 5\%$ of the activity in the starting material 16.

**3,3-Diphenyl-1-benzenesulfonamidopropane-2-$^{14}C$ (9) from 1-Benzenesulfonyl-2-(bromomethyl)ethylenimine-2-$^{14}C$ (8).** The labeled ethylenimine 8 (10.0 g, or 36.1 mmol; $(7.0 \pm 0.2) \times 10^8$ dpm/mol) was refluxed for 3 h with benzene (142 mL) containing 7.2 g (50 mmol) of aluminum chloride. The cooled reaction mixture was shaken with concentrated hydrochloric acid (36 mL), after which the aqueous layer was extracted with several portions of ether. The combined organic phases were washed with water, saturated bicarbonate solution, and finally water before being dried. Removal of the volatiles left a residue, which was crystallized from 95% ethyl alcohol to give 5.1 g of 3,3-diphenyl-2-benzenesulfonamidopropane-2-$^{14}C$ (9), mp 111–120 °C. Recrystallizations from the same solvent gave rise to pure material (2.8 g, 22%; mp 125–127 °C) showing only a single spot on a thin-layer chromatography plate. The product 9 assayed for $(7.00 \pm 0.13) \times 10^8$ dpm/mol, a value corresponding to complete retention of radioactivity: NMR ($CDCl_3$) $\delta$ 7.50 (m, 15, Ar H's), 5.00 (*t*, $J$ = 5.0, 1, NH), 3.90 (*t*, $J$ = 5, CH), 2.85 (q as $AX_3$, $J$ = 5, 2, $CH_2$), 2.18 (q as $AX_3$, $J$ = 5, 2, $CH_2$).

**Benzophenone (10) from 3,3-benzenesulfonamidopropane-2-$^{14}C$ (9).** The sulfonamide 9 (1.0 g or 3.0 mmol), as a solution in water (32 mL), and pyridine (14 mL) containing potassium permanganate (2.8 g) and sodium hydroxide (7.2 g), were refluxed for 3 h. This reaction mixture was treated essentially as described before[2] for the permanganate oxidation of diphenylacetaldehyde semicarbazone to benzophenone. The benzophenone in the form of its semicarbazone was obtained after one crystallization from 1:1 methanol–water with a melting point of mp 164–165 °C (0.20 g, 30%) and after a second crystallization with the same melting point (0.14 g, 20%). The semicarbazone was radioactive to an extent of $(4.5 \pm 0.2) \times 10^6$ dpm/mol; in other words, it retained less than 1% of the activity of the starting material.

In pilot runs, the identity of the benzophenone from the oxidation was checked by noting its melting point of 48–49 °C as well as that of the semicarbazone (mp 164.5–165.5 °C). The

analyses for C, H, and N were correct. With chromium trioxide in hot acetic acid, the yield of benzophenone was 15–20%.

**1-Benzenesulfonyl-2-benzylethylenimine (6).** The methyl ester **18** of *dl*-β-phenylalanine was recovered from its hydrochloride salt [12] and was reduced with lithium aluminum hydride essentially according to the procedure used before with the ethyl ester.[8] The reduction product, 3-phenyl-2-amino-1-hydroxypropane (**19**; 1.0 g, 6.6 mmol) was dissolved (cooling) in pyridine (20 mL) containing benzenesulfonyl chloride (2.9 g 16 mmol), and the solution was held at 5 °C overnight. Ice was added (50 g) followed by cold 4 N hydrochloric acid. The resulting solid was collected and crystallized from 95% ethyl alcohol to give 1.9 g (66%) of 3-phenyl-2-benzenesulfonamido-1-(benzenesulfonyloxy)propane (**20**), mp 104.5–106.5 °C.

Anal. Calcd for $C_{21}H_{21}NO_5S_2$: C, 58.47, H, 4.87. Found: C, 58.62; H, 4.87.

A mixture of the dibenzenesulfonyl derivative **20** (5.0 g, 10 mmol) with 48% hydrobromic acid (30 mL) in 200 mL of ethyl alcohol (95%) was refluxed for 3 h. The cooled reaction mixture, now containing 3-phenyl-2-benzenesulfonamido-1-bromopropane (**5**), was neutralized with 5% aqueous sodium hydroxide diluted with cold water (300 mL) and then treated with 185 mL of 5% sodium hydroxide. After 15 min of stirring the alkaline mixture, the white precipitate was collected and crystallized from alcohol to furnish 1-benzenesulfonyl-2-benzylethylenimine (**6**; 2.2 g, 66%) as needles, mp 51–53 °C (lit.[8] mp 55–56 °C).

Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.90; H, 5.53. Found: C, 66.04; H, 5.45.

Direct cyclization of the dibenzenesulfonyl compound **20** gave the desired product, but the yield was far lower.

***N*-Cinnamylbenzenesulfonamide (4).** The procedure for preparing cinnamyl derivative **4**, mp 89–90 °C (lit.[1] mp 89–90 °C), according to the Gabriel method was essentially the same as described before[1] except that cinnamyl bromide was used in the preparation of *N*-cinnamylphthalimide instead of cinnamyl chloride.

**3-Phenyl-2-bromo-1-benzenesulfonamidopropane (23).** A mixture of 2-benzylethylene oxide[9] (10.0 g, 70 mmol) and concentrated aqueous ammonia (260 g) was stirred for 72 h, during which period the mixture became homogeneous. After the water and excess ammonia were distilled off the remaining oil was taken up in benzene and dried. Distillation furnished 7.4 g (66%) of 3-phenyl-2-hydroxy-1-aminopropane (**21**), bp 130–132 °C (2.6 mm).

Anal. Calcd for $C_9H_{13}NO$: C, 71.52; H, 8.61. Found: C, 71.72; H, 8.60.

This intermediate **21** (5.0 g, 30 mmol) in pyridine solvent was dibenzenesulfonylated with benzenesulfonyl chloride essentially by following the procedure for the formation of 3-phenyl-2-benzenesulfonamido-1-(benzenesulfonyloxy)propane (see above). The temperature was adjusted at −5 °C to + 37 °C. The dibenzenesulfonyl derivative **22** was crystallized from 95% ethyl alcohol as white flakes weighing 11 g (80%) and melting at 121–123 °C.

Anal. Calcd for $C_{21}H_{21}NO_5S_2$: C, 58.47; H, 4.87. Found: C, 58.69; H, 5.05.

The benzenesulfonyloxy group was replaced with bromine by heating the dibenzenesulfonyl derivative **22** (10 g, 20 mmol) with 48% hydrobromic acid (59 mL) in 200 mL of ethanol. The procedure was similar to the one developed for the formation of 3-bromo-2-phenyl-1-benzenesulfonamidopropane (**25**) as outlined below. The desired product, 3-phenyl-2-bromo-1-benzenesulfonamidopropane (**23**), mp 69–70 °C after crystallization from benzene, was obtained in 36% yield.

Anal. Calcd for $C_{15}H_{16}BrNO_2S$: C, 50.85; H, 4.52; Br, 22.26. Found: C, 50.19; H, 4.38; Br, 22.71.

**3-Bromo-2-phenyl-1-benzenesulfonamidopropane (25).** Ethyl α-phenylcyanoacetate[13] (50 g, 0.26 mol) in 200 mL of dry ether was added dropwise over a period of 30 min to a stirred ice-cold solution of lithium aluminum hydride (50 g, 1.5 mol) in 1500 mL of ether. Stirring at 0 °C was continued for another 30 min before addition of crushed ice to decompose unused reagent. The mixture was taken to dryness at reduced pressures, and the dry solids were extracted with three 500-mL portions of boiling ethyl alcohol. The residue left after all volatiles were stripped from the combined alcohol extracts was dissolved in either and the solution dried. Distillation gave viscous, oily 3-hydroxy-2-phenyl-1-aminopropane [**24**, bp 112 °C (0.95 mm)] which crystallized to a hard white solid: 14.6 g (37%); mp 89–91 °C.

Anal. Calcd for $C_9H_{13}NO$: C, 71.72; H, 8.60. Found: C, 70.91; H, 8.50.

The combination of this intermediate **24** (5.0 g, 30 mmol) with 15 g (80 mmol) of benzenesulfonyl chloride in pyridine solvent (50 mL) closely followed the procedure used for the formation of 3-phenyl-2-benzenesulfonamido-1-(benzenesulfonyloxy)propane (**20**). Three crystallizations of the product from 95% alcohol yielded crystals of 3-phenyl-2-benzenesulfonamido-1-(benzenesulfonyloxy)propane: 7.5 g (52%); mp 89–92 °C.

Anal. Calcd for $C_{21}H_{21}NO_5S_2$: C, 58.47; H, 4.87. Found: C, 58.28; H, 4.92.

This dibenzenesulfonyl derivative (7.0 g, 16 mmol) together with 42 mL of 48% hydrobromic acid and 140 mL of 95% ethyl alcohol was boiled for 5 h. Concentration under reduced pressure left a residue, which was extracted thoroughly with ether. The extract was rinsed with several portions of water, dried, and then freed of all volatiles. Crystallization of the remaining material from ethyl alcohol furnished white crystals of 3-bromo-2-phenyl-1-benzenesulfonamidopropane (**25**): 4.7 g (96%); mp 68–70 °C. Thin-layer chromatography developed only one spot ($R_f$ 0.32 with benzene solvent).

Anal. Calcd for $C_{15}H_{16}NO_2S$: C, 50.82; H, 4.52; Br, 22.60. Found: C, 51.33; H, 4.70; Br, 22.14.

**3-Phenyl-2-benzenesulfonamido-1-bromopropane (5).** This product, prepared as described before,[8] showed a melting point of 22–23 °C (lit.[8] mp 22–23 °C) and was homogeneous according to TLC ($R_f$ 0.43 with benzene solvent).

**1,3-Diphenyl-2-benzenesulfonamidopropane (7).** This 1,3-diphenyl compound (**7**) was prepared by combining 2 mol of phenylmagnesium bromide with 1-benzenesulfonyl-2-(bromomethyl)ethylenimine as in **8** → **16** (see above).

**2,3-Diphenyl-1-benzenesulfonamidopropane (29).** α-Phenylcinnamonitrile[14] (10.0 g, 49 mmol) dissolved in dry ether was added to a stirred refluxing mixture of lithium aluminum hydride (5.6 g, 0.15 mol) in ether over a period of 20 min. Refluxing was continued for 4.5 h. After excess reagent had been decomposed with wet ether, concentrated hydrochloric acid was added, and the aqueous acid layer was washed with ether. The combined ether phases were rinsed with water, and the several pooled aqueous layers containing the hydrochloride salt of 2,3-diphenyl-1-aminopropane were processed as described below.

The ether solutions were shaken with aqueous sodium bicarbonate solution and then with water before drying and removal of all solvent. The residual oil consisted of analytically pure, homogeneous 2,3-diphenylpropionaldehyde (**28**):[15] 7.7 g 75%) IR 1725 $cm^{-1}$; $n^{26}_D$ 1.5748.

Anal. Calcd for $C_{15}H_{14}O$: C, 85.71; H, 6.67. Found: C, 85.67; H, 6.85.

The oxime was prepared by maintaining a solution of the 2,3-diphenylpropionaldehyde (**28**; 10.0 g, 48 mmol) and hydroxylamine hydrochloride (5.0 g, 70 mmol) in pyridine (25 mL) at 100 °C for 5 h. The solution was poured over 300 g of crushed ice, and the mixture, made acid with hydrochloric acid, was extracted thoroughly with ether. The extracts were shaken with several portions of water, dried, and stripped of solvent. The faintly yellow remaining oil was dried further by azeotroping with benzene and again was stripped of volatiles to yield the viscous oily oxime (7.5 g, 70%) showing two spots on a thin-layer chromatography plate ($R_f$ 0.82 and 0.93 with benzene): IR (neat) 3300, 1600 $cm^{-1}$; NMR ($CCl_4$) δ 8.83 (br s, 1, OH), 7.05 (m, 11, Ar H's plus CH=N), 3.68 (m, 1, CH), 3.05 (unsymm q, $J$ = 6, 2, $CH_2$).

For reduction of the oxime to the corresponding amine, a stirred suspension of lithium aluminum hydride (0.48 g, 13 mmol) in dry ether (150 mL) to which the above oxime (2.9 g; 13 mmol) had been added was refluxed for 12 h. Excess reagent was decomposed

(12) Brenner, M.; Huber, W. *Helv. Chim. Acta* **1953**, *36*, 1109.
(13) Horning, E. C.; Finelli, A. F. "Organic Syntheses"; Rabjohn, N., Ed.; Wiley: New York, 1963; Collect. Vol. IV, p 461.
(14) Buu-Hoi, N. P.; Xuong, N. D. *Bull. Soc. Chim. Fr.* **1957**, 650.
(15) See: Burton, H.; Shoppee, C. W. *J. Chem. Soc.* **1937**, 546. Also cf.: Stoermer, R.; Thier, C. *Chem. Ber.* **1925**, *58*, 2607.

with ice, and the mixture was acidified with hydrochloric acid. The aqueous layer containing the amine hydrochloride was washed with several portions of ether and then treated as described below.

Isolation of the hydrochloride of 2,3-diphenyl-1-aminopropane (27) from its water solution proceeded by removing all volatiles. The drying was completed by repeated azeotropic distillations with benzene. The product was extracted by boiling the dry mixture with 100 mL of chloroform for 5 min. The filtered chloroform solution was stripped of solvent, and the residue was crystallized from concentrated hydrochloric acid (12 mL). The resulting white neeldes of 2,3-diphenyl-1-aminopropane hydrochloride showed a melting point of 187–188 °C (lit.[16] mp 188–190 °C).

Anal. Calcd for $C_{15}H_{18}ClN$: C, 72.72; H, 7.27. Found: C, 72.38; H, 7.21.

The yield of hydrochloride **27** as obtained directly from cinnamonitrile **26** was 8%; the yield via the oxime was 31%.

Stirring the hydrochloride (1.2 g, 5.0 mmol) of 2,3-diphenyl-1-aminopropane (**27**) with benzenesulfonyl chloride (1.2 g, 7.0 mmol) and excess 5% aqueous sodium hydroxide for 10 h at room temperature afforded the corresponding sulfonamide. Two crystallizations from methanol gave white crystals (1.0 g, 61%) of 2,3-diphenyl-1-benzenesulfonamidopropane (**29**, mp 94–98 °C) which was homogeneous according to TLC.

Anal. Calcd for $C_{21}H_{21}NO_2S$: C, 71.70; H, 5.98. Found: C, 71.62; H, 5.97.

**Exposure of Test Compounds to the Action of Aluminum Chloride in Benzene.** All the experiments were performed by following the same general procedure as described above for the reaction with radioactive 1-benzenesulfonyl-2-(bromomethyl)-ethylenimine (**1**). The molar ratio of substrate to catalyst was held close to 1.5:1, and the amount of benzene corresponded to 3.8–4.4 mL/mmol of substrate. The 3,3-diphenyl-1-benzenesulfonamidopropane product was routinely characterized by its melting point and mixture melting point as well as by comparison of the proton magnetic resonance and infrared absorption curves. Thin-layer chromatography was frequently employed. The yield from the several test compounds as given in Table I should be compared to the 20–30% yields of 3,3-diphenyl-1-benzenesulfonamidopropane obtained from 1-benzenesulfonyl-2-(bromomethyl)ethylenimine.

(16) Freund, M.; Remse, P. *Chem. Ber.* **1890**, *23*, 2859.

**Acknowledgment.** We acknowledge with thanks the valuable discussions with John F. Lorand and the occasional participation of Frederick Karol. We are grateful to the Society of the Sigma Xi and to Watumull Foundation, Honolulu, for providing funds in partial support of this work.

**Registry No.** **1**, 78515-28-3; **3**, 78515-29-4; **4**, 78515-30-7; **5**, 78515-31-8; **6**, 78515-32-9; **7**, 78515-33-0; **8**, 78515-34-1; **9**, 78515-35-2; **10**, 119-61-9; **10** semicarbazone, 14066-73-0; **12**, 34541-67-8; **13**, 78529-86-9; **14**, 78515-36-3; **15**, 78515-37-4; **16**, 78515-38-5; **18**, 15028-44-1; **19**, 1795-98-8; **20**, 78515-39-6; **21**, 50411-26-2; **22**, 78515-40-9; **23**, 78515-41-0; **24**, 62247-39-6; **25**, 78515-42-1; **26**, 2510-95-4; **27**·HCl, 40692-28-2; **28**, 2016-03-7; **28** oxime, 78515-43-2; **29**, 78515-44-3; paraformaldehyde, 50-00-0; 1,3-bis(benzenesulfonyloxy)-2-benzenesulfonamidopropane-2-$^{14}C$, 78515-45-4; benzenesulfonyl chloride, 98-09-9; bromobenzene, 108-86-1; benzoic acid, 65-85-0; 2-benzylethylene oxide, 4436-24-2; ethyl α-phenylcyanoacetate, 4553-07-5; benzenesulfonyl-2-(bromomethyl)ethylenimine, 5120-12-7.

# *Notes*

## Kinetic Acetonation of Sucrose: Preparative Access to a Chirally Substituted 1,3,6-Trioxacyclooctane System[1]

Elisabeth Fanton, Jacques Gelas, and Derek Horton*

*Groupe de Chimie organique 1, Université de Clermont-Ferrand, Ensemble Scientifique des Cézeaux, 63170 Aubière, France, and the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210*

Horst Karl, Riaz Khan, C.-Kuan Lee, and Gita Patel

*Tate and Lyle Limited, Group Research and Development, Philip Lyle Memorial Research Laboratory, University of Reading, Reading, Great Britain RG6 2BX*

*Received February 13, 1981*

Acetonation (O-isopropylidenation) of sugars and their derivatives constitutes one of the most widely used modes for the protection of selected diol groups in sugar-based syntheses.[2] The conventional method for the preparation of such acetals employs acid catalysis under conditions wherein thermodynamic control prevails. Numerous mono- and polyisopropylidene acetals of monosaccharide sugars find application as routine intermediates in synthesis,[2,3] and the general factors that determine the structures of the favored products, through competition between the various available hydroxyl groups and different tautomeric forms of the sugar, are well understood.[4] Nevertheless, the standard preparative conditions, usually employing acetone in excess as the solvent, plus an acid catalyst, generally in the presence of anhydrous copper(II) sulfate, limit the accessible products to those preponderant at thermodynamic equilibrium. Acid-labile bonds in the carbohydrate derivative are broken during the reaction. Thus, the acetonation of sucrose (β-D-fructofuranosyl α-D-glucopyranoside, **1**)[5] under standard conditions leads solely to the normal products of acetonation of the constituent monosaccharides,[6] namely, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) and 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**3**); the acid-sensitive acetal bond of the disaccharide is broken, and the ring size of each sugar component is changed.

A method for acetonation of sugars developed in one of our laboratories[7-10] allows the introduction of *O*-isopropylidene groups under exclusively kinetic conditions

(1) Supported, in part, by RCP 529 of the CNRS, and NIH Grant GM-11976.

(2) DeBelder, A. N. *Adv. Carbohydr. Chem.* **1965**, *20*, 219–302; *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 179–241.

(3) Brady, R. F., Jr. *Adv. Carbohydr. Chem. Biochem.* **1971**, *26*, 197–278.

(4) Foster, A. B. In "The Carbohydrates"; Pigman, W., Horton, D., Eds.; Academic Press: New York, 1972; Vol. IA, pp 391–402.

(5) Khan, R. A., *Adv. Carbohydr. Chem. Biochem.* **1976**, *33*, 235–294.

(6) Fischer, E. *Ber.* **1895**, *28*, 1145–1167.

(7) Wolfrom, M. L.; Diwadkar, A. B.; Gelas, J.; Horton, D. *Carbohydr. Res.* **1974**, *35*, 87–96.

(8) Gelas, J.; Horton, D. *Carbohydr. Res.* **1975**, *45*, 181–195.

(9) Gelas, J.; Horton, D. *Carbohydr. Res.* **1978**, *67*, 371–387; **1979**, *71*, 103–121; *Heterocycles* **1981**, *16*, *in press*.

(10) Fanton, E.; Gelas, J.; Horton, D. *J. Chem. Soc., Chem. Commun.* **1980**, 21–22.

0022-3263/81/1946-4057$01.25/0 