Molecular Sieve Fluorination of Fluorobenzene Using Elemental Fluorine

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A new technique of fluorination which uses molecular sieves has been developed. Using elemental fluorine and this technique, monofluorination of fluorobenzene has been achieved with yields in excess of 19%. Under the optimum fluorinating conditions, the *o*- and *p*-difluorobenzenes were formed to the exclusion of meta. The polymers usually observed when using elemental fluorine were not found due to the localization of the substrate on the molecular sieves.

The study of direct fluorination of organic compounds was first attempted by Moissan[1] in 1886. Bockemuller[2] studied direct liquid-phase fluorination of aromatic compounds resulting primarily in the formation of addition products and polymers. Recently, Grakauskas[3] made a study of direct liquid-phase fluorination of several aromatic systems with limited success. Young[4] used thermochemical data to explain the failure of earlier workers. A 1961 publication of Baker and Eng[5] showed how molecular sieve beds could be employed in the chlorination of selected hydrocarbons.

The use of a molecular sieve bed in the fluorination of organic molecules interested the authors for the following reasons. In earlier reactions between elemental fluorine and organic molecules, complex mixtures were usually produced via progressive fluorination, cleavage, and in most cases polymerization. The present process gives a clean conversion to difluorobenzenes. If a respectable yield of monofluorinated product is to be obtained, the polymer formation should be reduced to a minimum. Through the use of molecular sieve beds it is possible to localize the substrate and hold it in a particular location throughout the fluorination, thereby preventing substrate radicals from coming into contact with other substrate molecules. Since such contact is necessary for polymerization, the desired effect should be achieved.

Earlier workers have ascribed the molecular degradation found during fluorination to the very exothermic nature of reactions between organic compounds and elemental fluorine. It has been found that fluorination reactions can be better controlled by leading the excess heat away from the reaction site. If the molecular sieves are maintained at low temperature throughout the fluorination, they could function as a third body and thereby dissipate the heat.

Since the substrate molecules are held stationary on the rather large surface area of the molecular sieve, any exothermic heat generated by the fluorination would be spread evenly over the entire molecular sieve surface, thereby preventing the development of localized hot spots.

Experimental Section

Fluorine is extremely hazardous primarily because the weak F–F bond in molecular fluorine (37.6 kcal/mol) leads to extraordinary reactivity. Based on our experience using elemental fluorine the following major safety precautions are recommended. Fluorine cylinders should be kept behind steel barricades and the valve operated remotely. Monel valves or high-nickel steel valves with Teflon packing are highly recommended. Stainless steel or Monel tubing (properly passified) is recommended for transfer of the gas. The reactor should be shielded and all lines containing fluorine under pressure should be located behind a heavy barricade. The latter precaution eliminates a potential danger in the event of rupture of pressure lines.

Elemental fluorine was obtained from Allied Chemical Corp. in 6-lb steel cylinders and was passed through a sodium fluoride trap to remove hydrogen fluoride impurities before use. PCR, Inc., supplied the fluorobenzene and the *o*- and *m*-difluorobenzenes. Pierce Chemical Co. supplied the *p*-difluorobenzene. The molecular sieves (13X, $\frac{1}{16}$ in. diameter pellets) were a gift from the Linde Division, Union Carbide Corp.

Fluorine and nitrogen gases used in the reaction were measured by Hasting mass flowmeters. The flow rate of nitrogen and fluorine were regulated with Hoke Micro-mite valves.

The molecular sieve reactor was made from 14 in. of 2.5-in. o.d. copper tubing. In a typical reactor, 241 g of molecular sieve pellets were packed inside the reactor. Glass wool was placed at each end to prevent the molecular sieves from plugging the outlets. The tube endings outside the reactor were fitted with Hoke on–off diaphragm valves.

The oven used in loading and unloading the sieves was a tube furnace capable of receiving the reactor and having a maximum operating temperature of 600 °C.

During the course of this investigation the following procedures were carried out on a routine basis.

In the loading procedure (see Figure 1), the fluorobenzene vapor was flushed with nitrogen from the boiling flask, F, through valves, V_2 and V_3, onto the molecular sieve bed, which was previously heated to 200 °C. When the fluorobenzene began to condense into the cooled receiver, R, nitrogen was allowed to pass directly into the sieve bed in order to remove any unadsorbed substrate. The reactor was allowed to come to room temperature, and the apparatus was disassembled at tubing connectors, C_1 and C_2. The reactor was weighed and reassembled, as in Figure 2, in preparation for the fluorination. In the fluorinating procedure the reactor was cooled by dry ice, flushed with nitrogen, and then the prescribed amount of fluorine and nitrogen was allowed to pass through the respective flow transducers, FT, and through the trap, T, and into the reactor. Following this the reactor was flushed with nitrogen for 20 min to remove the excess fluorine.

In the unloading procedure an apparatus was used similar to that in Figure 1. The reactor was flushed with nitrogen at room temperature for 20 min and then the temperature was raised to 400 °C. The product was flushed from the reactor and condensed in receiver R, which was cooled by a mixture of dry ice and trichloroethylene.

Gas chromatography was used in the analysis of each reaction product. The conditions of analysis were similar to that of Seiler, Durrance, and Sams.[6] The retention times of fluorobenzene and of the three isomeric difluorobenzenes were identical with those of the authentic compounds. Through use of a disc integrator, peak areas were calculated and then compared to calibration curves which were obtained by using injections of known concentration.

Results

Early in this investigation, a series of experiments were carried out to determine the optimum fluorinating conditions based on the highest percent yield. Maintaining the fluorine to fluorobenzene ratio at 0.75, reactions were carried out at −185, −78, 25, and 100 °C following techniques similar to those described in the procedure. Since the percent of monofluorinated product was found to be 0.20, 5.87, 0.23, and 0.0%, respectively, −78 °C was considered to be the optimum reaction temperature. Additional experiments were carried out maintaining the fluorine to fluorobenzene ratio at 0.75 and the temperature at −78 °C while using different schedules for the introduction of fluorine. A series of experiments using both constant fluorine flow rates and stepwise increases in fluorine flow rates were conducted. These studies indicated that a flow rate of 10 mL of fluorine and 90 mL of nitrogen for the first hour, 20 mL of fluorine and 80 mL of nitrogen for the second hour, and 30 mL of fluorine and 70 mL of nitrogen for the third hour produced the highest percent of monofluorinated
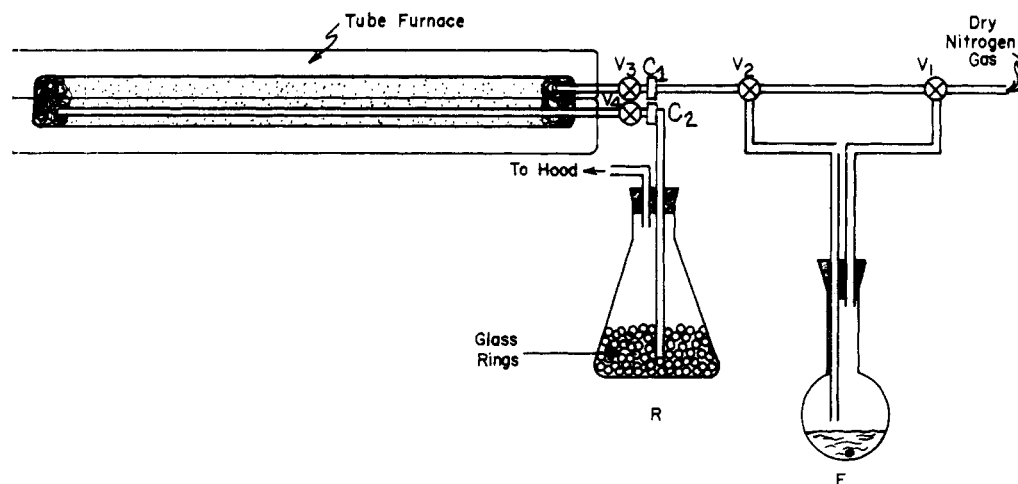
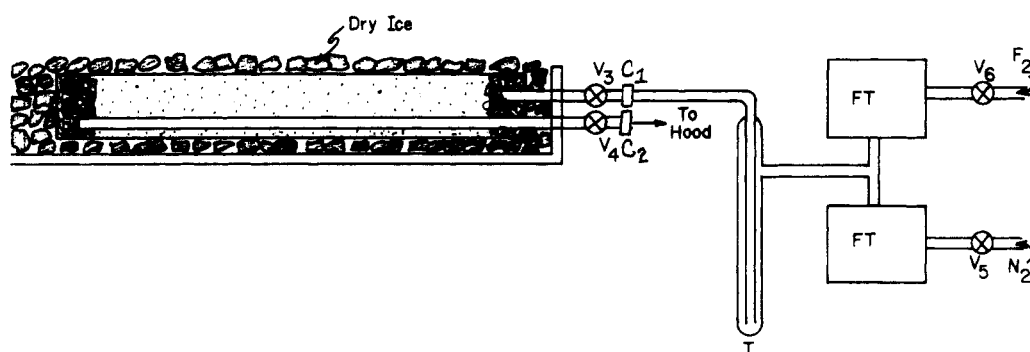**Figure 1.** Apparatus used for loading and unloading the molecular sieve bed.

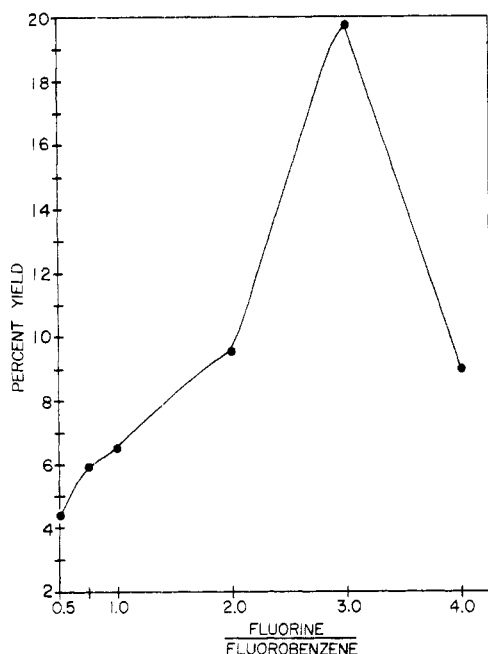**Figure 2.** Apparatus used for fluorinating the substrate while on the molecular sieve bed.

Figure 3.

Table I

Fluorine/	Difluorobenzene, % yield			
fluorobenzene[a]	Ortho	Meta	Para	Total
0.50	1.09	0.66	2.62	4.4
0.75	1.33	0.807	3.73	5.9
1.00	1.63	1.16	3.76	6.5
2.00	3.89	0.196	5.38	9.5
3.00	8.12	0	11.61	19.7
4.00	3.05	0	6.10	9.1

[a] The number of millimoles of fluorobenzene varied depending on the loading capacity of each individual reactor, the average being 280.

fluorine to fluorobenzene ratio was varied from 0.5 to 4.0. Table I and Figure 3 present the results of these experiments.

Discussion

Figure 3 shows that the percent difluorobenzene synthesized is increased from 4.4% when the ratio of fluorine to fluorobenzene was 0.5, hit a maximum of 19.7% when the ratio was 3, then decreased to 9.1% when the ratio was 4. This data shows that the highest efficiency with respect to the substrate occurs when the fluorine to fluorobenzene ratio is 3. Analysis of the substances recovered in the unloading procedure showed only fluorobenzene and the difluorobenzene isomers present.

Fluorination at the ratio of 3, as found in Table I, gave the highest percent overall yield of the difluorobenzenes, which was 19.7%. The remaining 80.3% of the product was unfluo-

products. This program of gradual increase in fluorine introduction was retained for the remaining experiments.

Attention was directed to determine the optimum fluorine to fluorobenzene ratio. Six reactions were carried out in which the temperature was maintained at −78 °C, the F_2 was introduced according to the 10/20/30 graded program, and the

rinated monofluorobenzene. Although significant amounts of meta isomer were found in experiments with fluorine to fluorobenzene ratios up through 2, it is interesting to note that no meta isomer was found when the fluorine to fluorobenzene ratios were 3 or greater. The fact that no polymers were found indicates that the technique used was successful in eliminating polymer formation.

Desirable characteristics inherent to the molecular sieve technique are: (1) substrate molecules are separated and localized, which ensures dimolecular reactions; (2) adsorptive properties of the molecular sieves permit loading and unloading a substance in a completely reversible fashion; (3) molecular sieves function as a third body to dissipate the heat of reaction; (4) heat of reaction is generated over a greater area; and (5) adsorbed substrate is not free to participate in polymer formation.

As may be seen from the procedure described earlier in this work, a complete fluorination can be carried out with minimal effort in a matter of hours. Although in a typical reaction the amount of products obtained are within the limits of experimental error, the molecular sieves were found to have lost approximately one-half of their active loading sites with each successive fluorination. Efforts to determine the cause of active site loss resulted in experiments which showed the endogenous hydrofluoric acid reacting with the silicates of the molecular sieves and reducing the number of loading sites. After several unsuccessful attempts to use the molecular sieves repeatedly, it was found that the gradual degradation of the molecular sieves represented an uncontrollable reaction parameter. In order to ensure reproducible results, each experiment in this study was begun with fresh unused molecular sieves, thereby overcoming the aforementioned difficulty.

Conclusion

Conditions have been optimized to form the greatest amount of difluorobenze product. Under the following conditions: temperature, −78 °C; fluorination schedule, 10/20/30; and fluorine to substrate ratio, 3; a maximum yield of 19.7% monofluorinated product was obtained. Despite the relatively high yield of desired products, there was no meta isomer found; however, measurable amounts of the meta isomer were observed in the experiments conducted at the lower ratios. The usual polymer formation, which is expected when elemental fluorine is allowed to react with organic substrates, was not observed due to aforementioned factors. Although this technique is easily accomplished, there is one drawback. The major difficulty lies in the fact that a completely inert molecular sieve has not been found; therefore, this work is being discontinued.

References and Notes

(1) H. Moissan, "Das Fluor und siene Verbindungen". Verlag M. Krayn, Berlin, 1900, p 236 ff.
(2) W. Bockemuller, *Justus Liebigs Ann. Chem.*, **506**, 20 (1933).
(3) V. Grakauskas, *J. Org. Chem.*, **35**, 723 (1970).
(4) J. A. Young, *J. Chem. Educ.*, **47**, 733 (1970).
(5) S. B. Baker, U.S. Patent No. 2 998 459 (1961).
(6) K. E. Sieler, M. A. Durrance, and L. C. Sams, *J. Chromatogr.*, **63** 375 (1971).

Notes

## Reactions of α-Alkoxy-α,β-unsaturated Carbonyl Compounds[1]

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α-Alkoxy-α,β-unsaturated carbonyl compounds have attracted our attention because of their potential as addends in annulation and addition reactions. The products of these reactions, α-alkoxycarbonyl compounds (e.g., 1), would be useful intermediates in the synthesis of natural products, e.g., cerin or β-ecdysone. It was uncertain, however, whether the unsaturated carbonyl of the addend would be sufficiently reactive to participate in the required reactions. Mesomeric electron donation from the alkoxy group[2] might make the system less susceptible to nucleophilic attack even as the carbonyl group is activating the alkene. As model compounds for study, we have chosen methyl α-methoxyacrylate (2) and 2-ethoxy-1-buten-3-one (3). We have investigated reactions of these compounds with nucleophiles (as a prelude to studies of the Robinson annulation), with lithium dialkylcuprates, and with dienes.
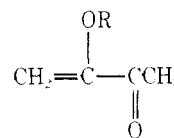
Compound 2 was prepared from methyl 2,3-dibromopropionate by the method of Ogata et al.[3] The enone 3, originally obtained by Harris as an unidentified side product in the preparation of 3,3-diethoxy-2-butanone (4),[4] was prepared
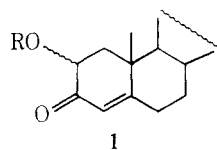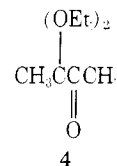

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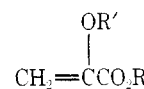
2, R = R′ = Me
6, R = Et; R′ = Me
7, R = R′ = Et

3, R = Et
5, R = Me

4

in our work by distilling ketal 4 from KHSO$_4$[5] (cf. the preparation of the methyl analogue, 5[6]).

Although reactions of nucleophiles with 6[7] and 7[8] have been reported, no successful conjugate addition to any of these compounds has yet been described. Attempts to induce the addition of the sodium enolates of cyclohexanone, methylcyclohexanone, dimedone, or 2-carbethoxycyclohexanone to 2 or 3 were unsuccessful. Dimethyl sodiomalonate, however, was an effective nucleophile toward both 3 and 2, giving 8 and 9, respectively. The best yields (60%) of 8 were obtained by refluxing an ether–methanol solution of 3, dimethyl malonate, and sodium methoxide for 24 h. By comparison, the analogous reaction with methyl vinyl ketone occurs within 2 h at room

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