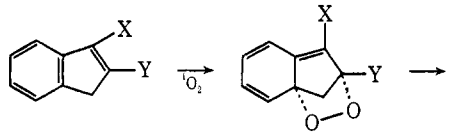
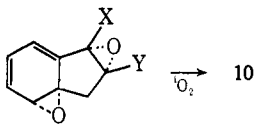
first step, giving **12**. Rearrangement of this highly strained peroxide to **13** is a reaction similar to one which proceeds readily at higher temperatures in less-strained systems.[20] Addition of a second singlet oxygen molecule to the resulting product would be rapid, to give **10**. Because of the mode of formation,



12

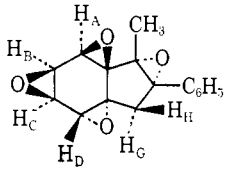


13

the epoxide groups are assigned to be cis; models show the top face is the less hindered, so that the peroxide bridge is suggested to be trans to the epoxides.

The intermediacy of **12** provides a rationale for the formation of compounds **6–8** as well. Rearrangement of **12** to the 2,3-dioxetane followed by cleavage has analogy,[20b] and would account for the formation of homophthalaldehyde and **8**; **6** and **7** could derive either from the dioxetane or from **12** directly by nucleophilic attack followed by allylic shift.

The behavior of compound **10d** on heating provides further evidence for the assigned structure. Warming gives rapid rearrangement to a mixture of two compounds, of which the major (>70% by nmr) product, an isomer by analysis and mass spectrum, had mp 184.5–186°; the compound has neither C=O nor OH bands in the ir; nmr shows no peaks (except phenyl) below 3.8 ppm. The spectrum and its analysis are summarized in Tables I and II. On the basis of its spectra and analogy, the compound was assigned the tetraepoxide (*benzene trioxide!*) structure **14**. The ^{13}C spectra agree with the assignment.[19] An exactly analogous rearrangement in a simpler system has been found by Foster and Berchtold.[21] Nmr chemical shifts of **14** agree well with the values of these authors.



14

Compounds **10a–c** undergo similar rearrangements in good yield. The stereochemistry is assigned as shown consistent with that of **10d**; only in this stereochemistry do protons A and C but not B and D have the W arrangement required for long-range coupling.[22] These novel compounds are all produced in synthetically useful yields. The above experiments make it less likely that **6** and **7** are derived from any intermediate related to the ene reaction.[8c] The greater rate of photooxidation of indene at low temperature suggests that the formation of **12** may be reversible at higher temperatures; attempts to trap **12** are in progress.

(20) (a) J. Boche and O. A. Rundquist, *J. Org. Chem.*, **33**, 4285 (1968); (b) J.-P. LeRoux and J.-J. Basselier, *C. R. Acad. Sci. Paris*, **271**, 461 (1970).

(21) C. H. Foster and G. A. Berchtold, *J. Amer. Chem. Soc.*, **94**, 7939 (1972). We thank Professor Berchtold for a prepublication copy of his manuscript.

(22) Other formulations in which some of the oxygen bridges are not epoxides are less likely because they would be expected to have nmr absorption at lower field for the α protons.

(23) Eastman Kodak Fellow, 1970–1971.

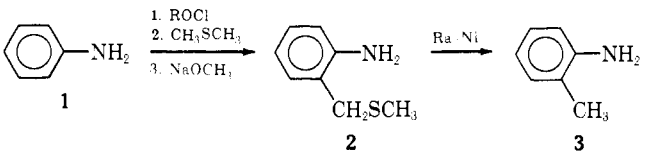
Christopher S. Foote,* Stephen Mazur[23]
Paul A. Burns, Duane Lerdal
Contribution No. 2953
Department of Chemistry, University of California
Los Angeles, California 90024
Received May 4, 1972

Specific Ortho Alkylation of Aromatic Amines

Sir:

Of the various methods available for the formation of C–C bonds to aromatic rings, the classical Friedel–Crafts reaction is undoubtedly the best known and the most widely used.[1] We now wish to describe a simple experimental procedure which permits the specific ortho alkylation of aromatic amines. The application of this process provides a superior method for the synthesis of certain isomerically pure polysubstituted aromatic compounds.

In a typical procedure, 1 equiv (*ca.* 0.1 mol) of *tert*-butyl hypochlorite[2] in 10 ml of methylene chloride[3] was added to a vigorously stirred solution of 1 equiv (*ca.* 0.1 mol) of aniline (**1**) in 400 ml of methylene chloride[3]



1 2 3

at −65°.[4] The reaction mixture was stirred for 25 min and 3 equiv of dimethyl sulfide was added dropwise at −65°.[4] The reaction mixture was stirred for 40 min and a solution of 1.2 equiv of sodium methoxide in 50 ml of methanol was added at −65°. The reaction mixture was stirred for 1 hr at −65°, warmed to room temperature, and worked up by standard procedures to give **2**. The structure of **2** was established on the basis of its spectroscopic properties and its facile conversion to **3** on reduction with Raney nickel at room temperature. Table I lists a series of aniline derivatives which have been converted to the corresponding 2-thiomethoxymethylanilines according to this procedure. As can be seen from Table I addition of the thiomethoxymethyl group occurs only in the position ortho to the amino function. Hence, ortho- and para-sub-

(1) C. Friedel and J. M. Crafts, *C. R. Acad. Sci.*, **84**, 1392, 1450 (1877). For a recent detailed account of the Friedel–Crafts reaction see G. A. Olah, "Friedel–Crafts and Related Reactions," Interscience, New York, N. Y., 1963–1965.

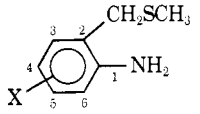
(2) In addition to *tert*-butyl hypochlorite, *N*-chlorosuccinimide and calcium hypochlorite (HTH) have been used as sources of chlorine in this reaction.

(3) The reaction can be run in a wide variety of solvents. Solvents as extreme in polarity as toluene and methanol have been used. Methylene chloride has been the most commonly used solvent.

(4) The reaction can be run over a broad temperature range. In part, the preferred temperature is dictated by the substituents on the aromatic ring, since these determine the stability of the intermediate *N*-chloroanilines[5] (*vide post*). The reaction can be run in the vicinity of 0°, but improved yields are obtained at lower temperatures.

(5) P. G. Gassman and G. Campbell, *J. Amer. Chem. Soc.*, **94**, 3891 (1972).

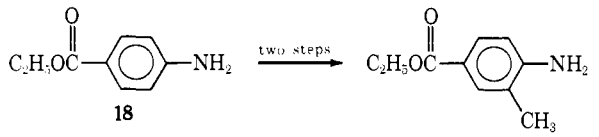
Table I. Conversions of Anilines into 2-Thiomethoxymethylanilines



Starting material	Products	% yield[a]	% conversion
Aniline (**1**)	**2**, X = H	90	82
p-Toluidine (**4**)	**5**, X = 4-CH_3	54	74
m-Toluidine (**6**)	**7**, X = 3-CH_3, + **8**, X = 5-CH_3	86	58
o-Toluidine (**9**)	**10**, X = 6-CH_3	41	86
p-Chloroaniline (**11**)	**12**, X = 4-Cl	83	75
m-Chloroaniline (**13**)	**14**, X = 3-Cl, + **15**, X = 5-Cl	87	49
o-Chloroaniline (**16**)	**17**, X = 6-Cl	70	37
Benzocaine (**18**)	**19**, X = 4-$CO_2C_2H_5$	65	*b*

[a] Based on unrecovered starting material. [b] No attempt was made to recover starting material in this case.

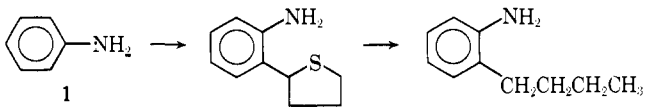
stituted anilines give only a single product, while meta-substituted anilines yield a mixture of products resulting from attack at each of the two available ortho positions. The balance between the two products is almost equal. For instance, in the reaction of **13**, the ratio of **14** to **15** was 3:2. In those cases where Raney nickel desulfurization was carried out the yields of the resultant *o*-toluidine derivatives ranged from 60 to 88% for the reduction. The utility of the overall process is illustrated by the conversion of **18** into **20** (*via* **19**) in 57%



18 20

yield. The specificity of the substitution represents a distinct advantage over the Friedel–Crafts reaction.

In principle, our process should permit the alkylation of the aromatic ring with substituents other than methyl. This concept was established in practice by the conversion of **1** into **21** in 64% yield when dimethyl sulfide



1 21 22

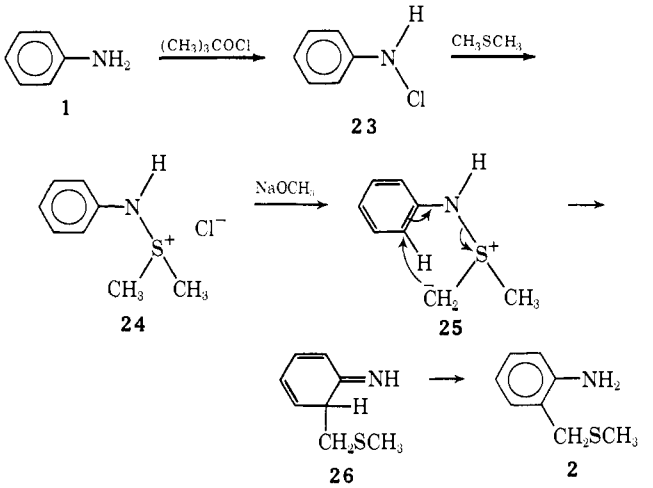
was replaced by tetramethylene sulfide in our general procedure. Raney nickel reduction of **21** gave **22** in 62% yield. In this way we could easily incorporate an *n*-butyl group stereospecifically in the ortho position of aniline. We know of no other way of cleanly accomplishing this type of conversion.

There is ample mechanistic precedence for each of the steps involved in the reaction described above.[6] As shown in Scheme I, the chlorinating agent converts the aniline (**1**) into the mono-*N*-chloroaniline (**23**).[5,7]

(6) We wish to stress that there are no new reactions involved in our overall process. Each of the steps involved has been described before. The significance of the communication resides in our developement of a process which combines these known reactions into a sequence which can be run in a short time with simple equipment and without the isolation of intermediates.

Addition of the sulfide to **23** produces the azasulfonium salt **24**.[8,10] Addition of base to the azasulfonium salts gives the ylide **25**,[8,11] which undergoes a facile Sommelet–Hauser type rearrangement to produce **26**.[12,13] Hydrogen transfer accompanied by rearomatization converts **26** into **2**.

Scheme I



As noted above, the process we describe occurs *via* a cyclic mechanism in which little, if any, charge develops on the aromatic ring. Thus, the reaction works equally well in the presence of electron-donating or electron-withdrawing substituents on the aromatic ring. This provides a distinct advantage over the classical Friedel–Crafts reaction. In summary, we feel that we have developed a simple process for aromatic substitution which will prove to be applicable to the synthesis of numerous aromatic compounds. Some examples of the application of our process are described in the following communications.[14]

Acknowledgment. We are indebted to the National Cancer Institute of the Public Health Service for Grant No. CA-07110 which partially supported this investigation.

(7) The formation of the mono-*N*-chloro derivative represents the key step in the overall process. We[8] and others[9] have previously described the ortho substitution of secondary anilines by this process. However, the usefulness of these secondary anilines is extremely limited. By comparison, the preparation of ortho-substituted primary anilines offers access to a wide variety of ortho-disubstituted aromatics because of the ease of replacing the primary amino group with other functions *via* diazotization.

(8) P. G. Gassman, G. Gruetzmacher, and R. H. Smith, *Tetrahedron Lett.*, 497 (1972).

(9) C. R. Johnson, C. C. Bacon, and W. D. Kingsbury, *ibid.*, 501 (1972).

(10) R. Appel and W. Büchner, *Chem. Ber.*, **95**, 849, 855 (1962).

(11) P. Claus and W. Vycudilik, *Monatsh. Chem.*, **101**, 396, 405 (1970); U. Lerch and J. G. Moffatt, *J. Org. Chem.*, **36**, 3861 (1971).

(12) M. Sommelet, *C. R. Acad. Sci.*, **205**, 56 (1937); G. C. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 3572 (1962); G. C. Jones, W. Q. Beard, and C. R. Hauser, *ibid.*, **28**, 119 (1963).

(13) M. G. Burdon and J. G. Moffatt, *J. Amer. Chem. Soc.*, **88**, 5855 (1966); **89**, 4725 (1967); J. Doucet and A. Robert, *C. R. Acad. Sci. Paris, Ser. C*, **272**, 1562 (1971); P. Claus, *Montash. Chem.*, **102**, 913 (1971); P. Claus, N. Vavra, and P. Schilling, *ibid.*, **102**, 1072 (1971).

(14) P. G. Gassman and T. J. van Bergen, *J. Amer. Chem. Soc.*, **95**, 590, 591 (1973).

Paul G. Gassman,* Gordon Gruetzmacher

Department of Chemistry, The Ohio State University
Columbus, Ohio 43210

Received October 4, 1972