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CONCERNING THE CHLOROMETHYLATION OF ALKYLBENZENES AND POLYSTYRENES BY CHLOROMETHYL METHYL ETHER

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Chloromethyl methyl ether-stannic chloride treatments of toluene, ethylbenzene, isopropylbenzene and tert-butyl benzene afforded respectively, 26.5, 16.8, 5.5 and 2.5% ortho-products. No meta-products could be detected (less than 0.5%). Similar chloroalkylation of linear polystyrenes followed by conversion of the chloromethyl groups to hydroxylmethyl, yielded products possessing 5.0 ± .3% ortho-substitution.

The introduction of the chloromethyl group onto aromatic rings[1] and into polystyrenes[2] via Friedel-Crafts conditions with various reagents has been a standard tool of organic chemistry for a long time. The importance of chloromethylated polystyrenes has been heightened recently by the widespread use of these materials in the Merrifield solid-phase peptide syntheses[3] (SPPS's), in solid-phase reagents for organic syntheses[4] and in polymer supported catalyst systems.[5] The most commonly employed procedure for introducing the chloromethyl group has been the use of chloromethyl methyl ether with stannic chloride as the catalyst.[2,3] With this procedure it has been noted that the level of substitution is difficult to control[6,7], that variable results are obtained from the same reagent mixture and resin[6,8] and that chloromethyl methyl ether is very carcinogenic.[9] Several alternative procedures to chloromethylated polystyrenes have been suggested.[6,7,10,11] One of these[11] is the copolymerization of styrene, divinylbenzene and available commercial 60:40 mixtures[12] of meta- and para-chloromethylstyrenes. However, in our NMR studies of a number of commercial functionalized resins over the last several years[13], we see no evidence at 125 MHz of the expected doublet $-^{13}CH_2Cl$ or $-^{13}CH_2OH$ carbon-13 signals that would be exhibited in products from the latter mode of preparation.[11] We are led to conclude that chloroalkylation is still the preferred mode for the initial substitution of these resins.

We have not been able to find any information regarding the positional selectivity of the reagent system chloromethyl methyl ether-$SnCl_4$ with simple aromatics and polystyrenes. Besides the fundamental importance of this sort of information, precise knowledge of the extent of ortho-CH_2Cl groups in chloromethylated resins might shed some light on why a small proportion of the CH_2Cl-group are sometimes less accessible to displacement reactions[14] even with the preferred amino acid cesium salt procedure[8,15] in the case of the initial step in SPPS's. We wish to report the investigation of the reaction of a set of alkyl benzenes and several linear polystyrenes with the above mentioned reagent system that demonstrates for the first time its regioselectivity.

The chloromethylation products of toluene, ethylbenzene, isopropylbenzene and tert-butylbenzene were determined by both ^1H and non-NOE ^{13}C NMR.[16] Reaction conditions were chosen

similar to those that have been employed previously for chloromethylation of polystyrene resins.[3,16] Conversion of the substrates was held to 10-20%, which may be thought of as corresponding to the level of substitution for polystyrene resins to be used in SPPS's.[14] At this level of conversion, the formation of more complicated multi-ring products is not significant and, in the case of linear and cross-linked polystyrene resins, the production of crosslinks is negligible. After decomposition of the catalyst with ice water, washing the organic phase with 1N HCl and drying the organic phase (over $MgSO_4$), the product mixtures were investigated by NMR.[16] In most cases the solvent chloroform, excess chloromethyl methyl ether and a major portion of the unreacted alkylbenzene were subsequently removed under vacuum and further NMR examinations made. The results for each substrate were obtained from 3 - 5 runs where the catalyst concentration varied over a range of 0.1 to 0.01 molar; no significant variations of ortho-para ratios were observed over this catalyst concentration range; it is possible that the yields changed but no precise conversion yield data was sought.

In the proton spectra of all product mixtures at 100 MHz, separate, but partially overlapping, $-CH_2Cl$ signals (one much more intense than the other) were evident; 500 MHz spectra provided even better resolution. Based on NMR study of model compounds[17], and products identified in some previous chloromethylation studies[18-20], the most intense proton signal can be assigned with some confidence to the para-isomer (and possibly any meta but even this signal should be resolved from ortho at 500 MHz) and the lower field, weaker signal to the ortho-isomer. In the non-NOE carbon-13 spectra at 125 MHz, two well separated (1.4 - 2.0 ppm) $-^{13}CH_2Cl$ signals, an intense one (para) and a higher field, weaker one (ortho) were always identifiable.[17] Spectra of model compounds and authentic samples in some cases suggested that the para- and meta $-^{13}CH_2Cl$ signals should be resolvable at 125 MHz[17] but careful scrutiny around the para signal under high gain and with various data filter selections did not reveal any features attributable to any other weak signal in the product mixtures. Spectral simulation calculations with a BASIC plot program were carried out with experimental line-widths, various para-meta chemical shift separations from model compounds and authentic samples, relative signal intensities from 20:1 to 500:1 and simulated random noise. From these results we are led to the conclusion that there must be less than 0.5% meta-isomer in all cases. The observed ortho-product percentages obtained from proton and non-NOE carbon-13 spectra agreed satisfactorily and have been averaged: toluene, 26.5 ± 1.1%; ethylbenzene 16.8 ± 0.8%; isopropylbenzene 5.5 ± .6%; tert-butylbenzene 2.5 ± 0.3%. These results can be compared with the only other published chloromethylation results for these substances[19] that utilized a reagent system of $CH_2=O$, HCl and $SnCl_4$: toluene, o-45.2%, m-1.1%; ethylbenzene, o-29.5%, m-1.9%; isopropylbenzene, o-12.1%, m-3.3%; tert-butylbenzene, o- about 0.1%, m-6.1%. In another study[20] it has been claimed that, as the $SnCl_4$ concentration is reduced by a factor of 14, the meta isomer content in the case of toluene drops from 4 to 1.5%, but the reagent system for which this was observed was not identified.

In the case of linear polystyrenes, the carbon signals for the $-^{13}CH_2Cl$ groups overlap the backbone ^{13}-CH and $-^{13}CH_2-$ signals so any much weaker, upfield signal due to ortho-$^{13}CH_2Cl$ would be impossible to detect in natural abundance. In this case the $-CH_2Cl$ resins were converted to $-CH_2OH$[21]. The 125 MHz carbon-13 spectra of these products exhibited a strong para-$^{13}CH_2OH$ signal (95.0 ± .8%) at 65.20 ppm and a weaker, upfield signal at 63.70 ppm which we

attribute to ortho-$^{13}CH_2OH$ (5.0 ± 0.8%). At the present time this latter assignment rests mainly on comparison of this carbon chemical shift with those for the $-^{13}CH_2OH$ groups in the α-hydroxylxylenes (p-65.16 ppm, m-65.30 ppm and o-63.40 ppm).[17] For lightly cross-linked polystyrenes one should expect a similar result. The broader carbon-13 linewidths for these resins make detection of the ortho percentage impossible in natural abundance.

The work presented here demonstrates for the first time that the chloroalkylation reagent chloromethyl methyl ether-$SnCl_4$ affords less than 0.5% meta-isomer but significant ortho-isomer for a series of alkyl benzenes and about 5% ortho upon treatment of linear polystyrenes.

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16. Conditions chosen were molar ratios of aromatic: chloromethyl methyl ether: catalyst about 3:1:0.1 with dilution in chloroform such that the catalyst concentration varied from 0.1 - .01 molar. All operations with chloromethyl methyl ether were carried out in a fume hood, using rubber gloves and eye protection. All aqueous phases from catalyst decomposition and material trapped (at dry ice or liquid N_2 temperature) during vacuum evaporations were treated with concentrated NaOH to insure destruction of any residual chloromethyl methyl ether. For ^{1}H NMR studies at 100 MHz, a small amount of TMS was added for locking; for 500 MHz ^{1}H and 125 MHz ^{13}C spectral studies, a portion of $CDCl_3$ or CD_2Cl_2 was added to the aliquot being examined by NMR to provide a deuterium lock signal.

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