[Contribution from the Chemistry Departments of Duquesne University
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THE REPLACEMENT OF METHOXYL GROUPS BY FREE ARYL RADICALS

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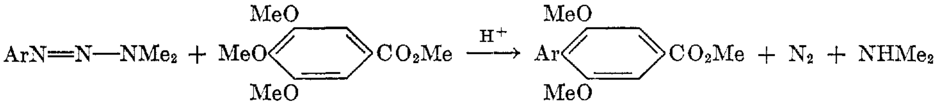
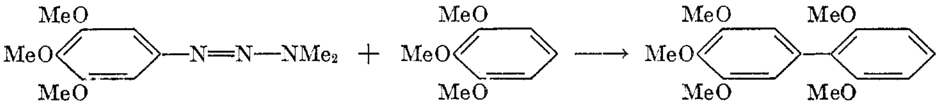
It has frequently been observed that alkoxyl groups may be displaced during Grignard reactions (1–3). In nearly all these cases the group displaced was in *ortho* or *para* position to a strongly electron-withdrawing group (CN, CO_2R, CHO etc.) and it may therefore be assumed that the attacking agent is the anion R^- derived from the Grignard reagent RMgX; the alkoxyl group must then be displaced as an alkoxide ion.

Elimination of methoxyl groups has also been observed (4, 5) as a side reaction in the reaction of aryl triazenes (I) with methyl 3,4,5-trimethoxybenzoate (II). The products thus formed were formulated as (III) on the supposition that methoxyl replacement occurs in the 4-position by analogy with the action of Grignard reagents on II. The main products of these reactions are however the "normal" products arising from replacement of hydrogen in the 2-position of II by the aryl group. By contrast, as has already been reported (6), the interaction of 3,3-dimethyl-1-(3,4,5-trimethoxyphenyl)triazene (IV) with 1,2,3-trimethoxybenzene (V) fails to yield the expected hexamethoxybiphenyl. The only product which could be isolated from this reaction (though in very poor yield) had the composition of a pentamethoxybiphenyl. It must therefore also have resulted from displacement of a methoxyl group.


I II III

It is generally considered [see *e.g.* (7)] that this reaction involves the free aryl radicals derived from the triazene; the observation of methoxyl displacement in the absence of an electron-withdrawing substituent further emphasized the difference in the mechanism of alkoxyl elimination operative here and in the above-mentioned Grignard reactions. The assignment of the constitutions (III) is therefore based on an analogy of doubtful validity and it was considered desirable to ascertain whether the free radical replacement also involves the central one of three vicinally placed methoxyl groups.


IV V VI

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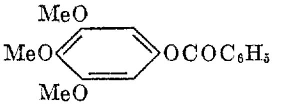
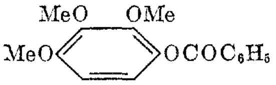
This has now been shown conclusively for the case of 2, 3′, 4′, 5′, 6-pentamethoxybiphenyl (VI) arising from IV and V; VI has also been obtained by an independent and unambiguous synthesis utilizing the Ullman reaction between 2-iodoresorcinol dimethyl ether and 5-iodopyrogallol trimethyl ether.

It further seemed desirable to confirm the absence of methoxyl displacement when Grignard reagents act on 1,2,3-trimethoxybenzene (V) and indeed we were unable to find any product from its reaction with phenylmagnesium bromide. We have however so far been unsuccessful in our attempt to find further examples of methoxyl replacement by free aryl radicals from different sources. The reaction of V with phenyl radicals from the reaction of phenylmagnesium bromide with bromobenzene in presence of colbaltous chloride yielded insufficient product to permit identification. It may, however, be noted here that two cases (8, 9) in which methoxyl displacement has been found to occur in Grignard reactions to a small extent in the absence of electron-withdrawing substituents may well have resulted from the formation of free radicals from the Grignard reagent under the very vigorous reaction conditions used.

The reaction of V with dibenzoyl peroxide did not lead to substitution by phenyl radicals but resulted instead in the introduction of benzoyloxy groups as has already been noted in the reaction of this reagent with phenols (10), and more recently with various naphthalene derivatives (11) and with polycyclic aromatic hydrocarbons (12). The present example is the first in which a phenolic ether is shown to behave in the same way. The products formed are VII and VIII, the former being obtained in much larger amount. The predominance of 5-substitution in this reaction is probably best attributed to its unusually strong dependence on steric influences (12).



VII



VIII

EXPERIMENTAL

2,3′,4′,5′,6-Pentamethoxybiphenyl. (*a*). A mixture of 3.3 g. of 3,3-dimethyl-1-(3,4,5-trimethoxyphenyl)triazene (IV) (6), 33 g. of 1,2,3-trimethoxybenzene (V), and 4 g. of glacial acetic acid was heated at 100° until nitrogen evolution ceased. The product was dissolved in ether, washed with dilute hydrochloric acid and caustic soda, dried, and distilled. After complete removal of trimethoxybenzene (below 130°/3 mm.), the residue was sublimed *in vacuo*. The product (VI) crystallized in colorless needles from methanol, m.p. 175–176°.

Anal. Calc'd for $C_{18}H_{22}O_6$: C, 64.6; H, 6.6; OCH_3, 55.7.
Calc'd for $C_{17}H_{20}O_5$: C, 67.1; H, 6.6; OCH_3, 51.0.
Found: C, 66.6; H, 6.5; OCH_3, 49.3.

(*b*). To a mixture of 0.5 g. (0.0021 mole) of 2-iodo-1,3-dimethoxybenzene and 0.55 g. (0.0021 mole) of 5-iodo-1,2,3-trimethoxybenzene, preheated to 210°, 1 g. of copper bronze was added rapidly in small portions. The temperature was then raised to 230° and maintained there for 30 minutes. After cooling, the product was extracted with benzene and crystallized on evaporation to a small bulk. Recrystallization from methanol furnished 2,3′,4′,5′,6-pentamethoxybiphenyl (VI) of m.p. 175–176°, undepressed on admixture with the product described under (*a*) above.

Anal. Calc'd for $C_{17}H_{20}O_5$: C, 67.1; H, 6.6.
Found: C, 67.3; H, 6.6.

Attempted reaction of 1,2,3-trimethoxybenzene with phenyl radicals. 1,2,3-Trimethoxybenzene (40 g.) and 1.5 g. of anhydrous cobaltous chloride were added to the Grignard reagent prepared from 2.5 g. of magnesium and 17 g. of bromobenzene in ether. Then 18 g. of bromobenzene was added dropwise. After leaving overnight, the mixture was refluxed (6 hours) to ensure complete reaction. The alkali-soluble portion of the product contained pyrogallol 1,3-dimethylether identified as its benzoate (m.p. 118° alone or when mixed with an authentic sample). The neutral fraction after removal of starting materials (and biphenyl) by vacuum distillation, left a dark oil from which only *p*-terphenyl could be isolated after chromatography on alumina.

Reaction of 1,2,3-trimethoxybenzene with benzoyl peroxide. A mixture of 40 g. of trimethoxybenzene and 10 g. of benzoyl peroxide was heated to 120° (bath temp.) until the vigorous reaction ceased. After cooling, a further 10 g. of benzoyl peroxide was added and the heating process was repeated, the temperature being finally raised to 160° for 10 minutes to ensure complete decomposition of the benzoyl peroxide. The cooled mixture was dissolved in ether, washed with sodium carbonate solution to remove benzoic acid, dried, and evaporated. After complete removal of unchanged trimethoxybenzene (100°/0.3 mm.) the residue was dissolved in 50:50 benzene-ligroin and chromatographed on alumina. The same solvent eluted the major portion of the products which were obtained as a pale yellow oil, which crystallized partially on standing. Recrystallization from methanol yielded colorless prisms (3.5 g.), m.p. 115–116°.

Anal. Calc'd for $C_{16}H_{16}O_5$: C, 66.7; H, 5.6.
Found: C, 66.7, 66.4; H, 5.8, 5.6.

This compound was identified as 3,4,5-trimethoxyphenyl benzoate (VII) by hydrolysis with aqueous alcoholic caustic soda to antiarol (3,4,5-trimethoxyphenol), obtained as colorless prisms from acetone, m.p. 146–147° [Literature (13), m.p. 147°] which was further converted to its acetate, m.p. 73–75° [Literature (13), m.p. 74°]. The remaining oil (approx. 2 g.) failed to crystallize and was therefore also hydrolyzed yielding a further quantity of antiarol (0.4 g.) together with an oil, which was shown to contain 2,3,4-trimethoxyphenol [derived from 2,3,4-trimethoxyphenyl benzoate (VIII)], by methylation with dimethyl sulfate and alkali to 1,2,3,4-tetramethoxybenzene, obtained as colorless prisms from cyclohexane, m.p. 86–88°.

SUMMARY

Methoxyl replacement is shown to occur in the reaction of 3,4,5-trimethoxyphenyl radicals with 1,2,3-trimethoxybenzene yielding 2, 3′, 4′, 5′, 6-pentamethoxybiphenyl.

The action of benzoyl peroxide on 1,2,3-trimethoxybenzene results in the introduction of the benzoyloxy group, chiefly in the 5-position.

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