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THE AMIDOALKYLATION OF AROMATIC HYDROCARBONS

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Abstract—The Nyberg procedure (the use of trifluoroacetic acid in chloroform) for the efficient amidoalkylation of aromatic hydrocarbons is limited to substrates more nucleophilic than benzene. The reaction involves protonation of the electrophile, cleavage to a carbonium ion and alkylation of the nucleophile by the carbonium ion. Either the cleavage step or the alkylation step may be rate-determining. The present work identifies some cases where a carbonium ion is formed but fails to alkylate the nucleophile (with benzene and nitro-substituted benzenes as nucleophiles) and other cases where the reaction conditions are not sufficient to permit cleavage of the protonated electrophile (the reactions of *N*-phthalimidomethylamides).

The amidoalkylation reaction may be thought of as a useful variation of the Mannich reaction, in which the amine moiety is replaced by an amide or an imide. This permits reaction with many compounds, e.g. benzene itself and benzenes having negative substituents, which are too weakly nucleophilic to participate in the Mannich reaction.

These reactions have been extensively reviewed.[1-3] The present report deals with the use of the amidoalkylation reaction to alkylate aromatic nuclei. These reactions are acid-catalyzed, and when the condensing agent is concentrated or fuming sulfuric acid the reaction is referred to as the Tscherniac–Einhorn reaction.[4] In a study of the acid-catalyzed reactions of *N* - formyloxymethyl - *N* - methylformamide,[5] it was noted that these reactions may be designated, in Ingold's classification, as belonging to the $A_{AL}1$ type,[6] in which a carbonium ion is formed in the rate-determining step. This designation, however, fails to indicate the many reaction subtleties, e.g. the effect of the reaction medium, the acid strength and the nature of the leaving group, which have been discussed by Zaugg.[2,3] There may be cases in which the carbonium ion is generated rapidly but reacts slowly or not at all with the nucleophile, i.e. cases in which the reaction of cation with nucleophile is rate-determining.

Sulfuric acid is the most commonly used and most generally effective acid catalyst and reaction medium. However, its use can lead to poor yields due to competing sulfonation, rearrangement and disubstitution. Of the many less vigorous reaction conditions that have been explored, Nyberg's[7] use of trifluoroacetic acid, occasionally with trifluoromethanesulfonic acid as a co-catalyst, in chloroform or methylene chloride as solvent, may be especially noteworthy. Although not as strong as sulfuric acid, trifluoroacetic acid is an acid of moderate strength, having a dissociation constant in water of 0.588 at 25°.[8] It has excellent solvent power for aromatic hydrocarbons, in general, and for all the electrophilic reagents of present interest. Its solubility in both polar and non-polar solvents and its low boiling point (72.4°) permits its facile separation from reaction mixtures. Finally, trifluoroacetate ion is almost certainly significantly less nucleophilic than sulfate ion, which is, in fact, only slightly less nucleophilic than acetate ion.[9] This low nucleophilicity for trifluoroacetate ion is suggested by the fact that trifluoroacetic acid is a preferred medium for the electrogeneration and stabilization of cation-radicals.[10]

A significant number of amidoalkylation reactions, using the Nyberg procedure, have been carried out in these laboratories. These experiments afford some useful insights into the scope and limitations of the Nyberg procedure and into the mechanism of these reactions.

RESULTS AND DISCUSSION

The results describing successful alkylations, with a variety of electrophiles, have been assembled in Table 1. The experiments commonly used 0.02–0.03 mole of both nucleophile and electrophile in 50 ml chloroform as solvent and with 25 ml trifluoroacetic acid as catalyst. In most cases the nucleophile was β-naphthol, pentamethylbenzene or mesitylene. The experiment with trifluoroacetic acid as both nucleophile and acid catalyst was carried out to demonstrate that, in the absence of other nucleophiles, *N* - (hydroxymethyl) - phthalimide, and presumably other amidomethylating agents as well, can be converted to the trifluoroacetoxymethyl compound and that the amidoalkylations may entail some equilibration between the initially added electrophile and the *N*-trifluoroacetoxymethyl compound formed from it.

Two experiments with nitriles as nucleophiles are also included in Table 1 to indicate that the Nyberg procedure can be used to prepare *N*-imidomethylamides. The reaction is convenient, although the yields obtained are not as good as those afforded by the sulfuric acid catalyzed reaction described by Buc.[11]

The *N,N'*-alkylidene- and *N,N'*-arylidenebisamides have diminished reactivity and will generally alkylate only reactive nucleophiles, e.g. phenols and anilides.[12] Nevertheless, trifluoroacetic acid catalysis permits reaction of both *N,N'*-methylenebisamides and *N,N'*-benzylidenebisamides with alkyl substituted benzenes, e.g. pentamethylbenzene and mesitylene. It should also be noted that the reaction of *N,N'*-benzylidenebisamides with benzene derivatives constitutes a direct synthetic route to substituted *N*-benzylhydrylamides and, on hydrolysis, to substituted *N*-benzhydrylamines.

2,6 - Diformyl - 2,6 - diaza - 4 - oxaheptane is also of interest for synthetic purposes. It is a difunctional electrophile, easily obtained by reacting *N*-methylformamide with paraformaldehyde and concen-

Table 1.

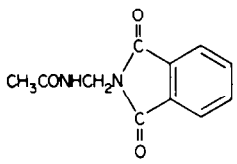
Electrophile	Nucleophile	Product	M.p. °C	Yield %	% N Calcd.	% N Fd.
N-(Hydroxymethyl)-2-pyrrolidinone	β-Naphthol	*N*-(2-Hydroxyl-1-naphthylmethyl)-2-pyrrolidinone	217–219	100	5.80	5.74
N-(Hydroxymethyl)-2-pyrrolidinone	Pentamethylbenzene	*N*-(Pentamethylbenzyl)-2-pyrrolidinone	111–113	87.0	5.71	5.57
N-(Hydroxymethyl)-2-pyrrolidinone	Mesitylene	*N*-(2,4,6-Trimethylbenzyl)-2-pyrrolidinone	62–64	83.0	6.45	6.33
N-(Hydroxymethyl)-phthalimide	Pentamethylbenzene	*N*-(Pentamethylbenzyl)-phthalimide	183–186	91.0	4.56	4.50
N-(Hydroxymethyl)-phthalimide	Mesitylene	*N*-(2,4,6-Trimethylbenzyl)-phthalimide	208–211	85.9	5.01	4.94
N-(Hydroxymethyl)-phthalimide	β-Naphthol	*N*-(2-Hydroxy-1-naphthylmethyl)-phthalimide	199–202	40.7		
N-(Hydroxymethyl)-phthalimide	Trifluoroacetic acid	*N*-(Trifluoroacetoxymethyl)-phthalimide	96–98	48.8	5.13	5.62
N-(Hydroxymethyl)-phthalimide	Acetonitrile	*N*-(Phthalimidomethyl)-acetamide	219–222	67.9		
N-(Hydroxymethyl)-phthalimide	n-Nonanenitrile	*N*-(Phthalimidomethyl)-n-nonanamide	133–136	60.8	8.85	8.76
2,6-Diformyl-2,6-diaza-4-oxaheptane	β-Naphthol	*N*-(2-Hydroxy-1-naphthylmethyl)-*N*-methylformamide	155–158	76.7		
2,6-Diformyl-2,6-diaza-4-oxaheptane	Pentamethylbenzene	*N*-Pentamethylbenzyl *N*-methylformamide	84–87	79.8		
N-Formyloxymethyl-*N*-methylformamide	β-Naphthol	*N*-(2-Hydroxy-1-naphthylmethyl)-*N*-methylformamide	159–161	84.9		
N-Ethoxymethyl-*N*-methylformamide	β-Naphthol	*N*-(2-Hydroxy-1-naphthylmethyl)-*N*-methylformamide	156–159	81.4		
N-Ethoxymethyl-*N*-methylformamide	Pentamethylbenzene	*N*-Pentamethylbenzyl-*N*-methylformamide	83–85	65.0	6.39	6.40
N-Ethoxymethyl-formamide	Pentamethylbenzene	*N*-Pentamethylbenzyl-formamide	204–205	82.9	6.82	6.70
Methylene-bis-acetamide	Pentamethylbenzene	*N*-Pentamethylbenzylacetamide	230–232	34.0		
Methylene-bis-benzamide	Pentamethylbenzene	*N*-Pentamethylbenzylbenzamide	192–197	92.9	4.98	5.28
Benzylidene-bis-acetamide	Pentamethylbenzene	*N*-(2,3,4,5,6-Pentamethylbenzhydryl)-acetamide	186–188	36.8	4.74	4.63
Benzylidene-bis-acetamide	Mesitylene	*N*-(2,4,6-Trimethylbenzhydryl)-acetamide	167–168	52.0	5.24	5.13

trated hydrochloric acid[13] and capable of reacting with two moles of nucleophile. It reacts readily with both β-naphthol and pentamethylbenzene and provides a convenient route to *N* - arylmethyl - *N* - methylformamides and to *N* - arylmethyl - *N* - methylamines.

The unsuccessful alkylation attempts, not shown in Table 1, provide some indication of the limitations of the Nyberg procedure using trifluoroacetic acid and chloroform. *N* - (Hydroxymethyl) - 2 - pyrrolidinone failed to alkylate both 2,4-dinitrophenol and *p*-nitrophenol. Attempts to alkylate *p*-nitrophenol with *N* - (acetoxymethyl) - 2 - pyrrolidinone were unsuccessful both with the standard procedure and in trifluoroacetic acid, undiluted by chloroform. Benzene was not alkylated by *N* - (hydroxymethyl) - 2 - pyrrolidinone, by *N* - (hydroxymethyl) - phthalimide or by 2,6 - diformyl - 2,6 - diaza - 4 - oxaheptane.

It is clear that in all of the foregoing unsuccessful experiments a cationic reagent was generated in the trifluoroacetic acid–chloroform system, since more nucleophilic substrates, e.g. pentamethylbenzene, are successfully alkylated. The failure to react must be attributed not to the failure to generate a carbonium ion but to more subtle distinctions such as the nature of the counterions associated with the cation, the degree to which the cation is free or associated and the nature of the medium in which the reaction is occurring. Nyberg[7] has shown that the addition of a cocatalyst, the stronger acid, trifluoromethanesulfonic acid, makes it possible to alkylate benzene with *N* - acetoxymethyl - *N* - methylformamide. It does not follow from this that a stronger acid is needed to generate the carbonium ion. We would argue that the addition of the stronger acid creates a more favorable environment for reaction and that this makes reaction with less nucleophilic species possible.

The results obtained with alkylidenebisamides and with *N* - (phthalimidomethyl) - amides are also illuminating. As noted in Table 1, pentamethylbenzene is successfully alkylated by methylene-bis-acetamide, by methylene-bis-benzamide and by benzylidene-bis-acetamide. However, attempts to alkylate pentamethylbenzene with *N* - (phthalimidomethyl) - acetamide, **1**, prepared as described by Buc,[11] gave only recovered starting materials, when the Nyberg procedure was used. This may seem surprising, since compounds related in structure to both halves of **1**, *N* - (hydroxymethyl) - phthalimide, *N* - ethoxymethyl - *N*- methylformamide and *N* - ethoxymethylformamide, all alkylate pentamethylbenzene in good yield. The structure of **1** is not in doubt. In addition, we have prepared *N* - (phthalimidomethyl) - *n* - nonanamide, **2**, and its NMR spectrum is completely consistent with the indicated structure. Both **2** and *N,N'* - methylene - bis -



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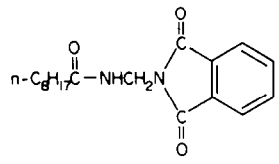

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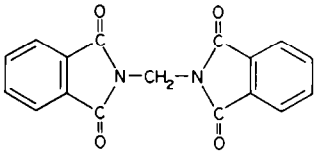
phthalimide, **3**, were recovered unchanged from attempts to alkylate pentamethylbenzene. In contrast, pentamethylbenzene was successfully alkylated by *N* - (2 - pyrrolidinonemethyl) - n - nonanamide, **4**, yielding 66.5% *N* - pentamethylbenzyl - 2 - pyrrolidinone and 8.2% *N* - pentamethylbenzyl - *n* - nonanamide.



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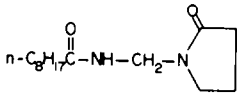

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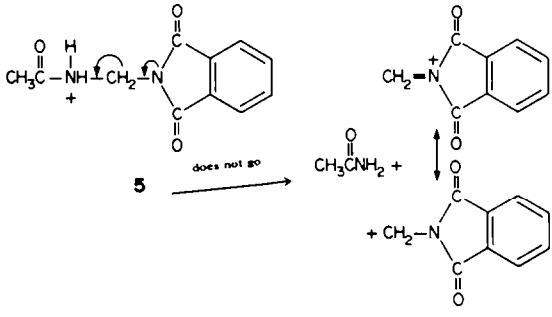
The inability of **1** to alkylate pentamethylbenzene is probably due to failure to form a carbonium ion under the reaction conditions. Protonation of the more basic amido nitrogen leads to the conjugate acid, **5**, but acetamide is such a poor leaving group that cleavage to form the phthalimidomethyl cation does not occur. Some anchimeric assistance from the phthalimidomethyl group is required but the imido nitrogen is too weakly basic to provide it. The same limitation obtains for **2**, and **3** may be



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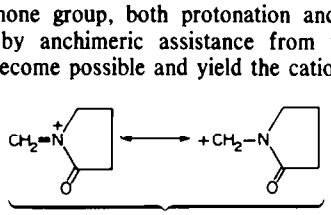
so weakly basic that it is not even protonated by trifluoroacetic acid in chloroform. With **4**, in which the phthalimido group of **2** is replaced by the more basic 2-pyrrolidinone group, both protonation and cleavage, promoted by anchimeric assistance from the lactam nitrogen, become possible and yield the cation, **6**.



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EXPERIMENTAL

N - (Hydroxymethyl) - 2 - pyrrolidinone was obtained from the Aldrich Chemical Company, Inc. and is available from their ABC-Library of Rare Chemicals. N - (Hydroxymethyl) - phthalimide,[11] 2,6 - diformyl - 2,6 - diaza - 4 - oxaheptane,[13] N - formyloxymethyl - N - methylformamide,[14] N - ethoxymethyl - N - methylformamide[15] and N - ethoxymethylformamide[16] were all prepared by previously reported methods.

Methylene-bis-acetamide. Acetamide (23.6 g, 0.4 mole), paraformaldehyde (3 g, 0.214 mole) and p-toluenesulfonic acid (0.5 g) in benzene (250 ml) were refluxed under a Dean-Stark trap until no further water separated. The benzene was removed at the water pump and the crude product was crystallized from ethanol; m.p. 195–197°; yield 7 g (26.9%).

Methylene-bis-benzamide. The above procedure applied to benzamide yielded 49.6% of methylene-bis-benzamide; m.p. 215–218° crystallized from ethanol.

Benzylidene-bis-acetamide. Acetamide (23.6 g, 0.4 mole) and benzaldehyde (21.2 g, 0.2 mole) in benzene (250 ml) were refluxed until no further water separated. This required 120 h. Removal of solvent and crystallization from ethanol yielded 33.5 g (81.3%) of benzylidene-bis-acetamide, m.p. 248–250°.

N - (*Acetoxymethyl*) - 2 - *pyrrolidinone.* A mixture of *N* - (hydroxymethyl) - 2 - pyrrolidinone (11.5 g, 0.10 mole), pyridine (9.8 g, 0.12 mole) and acetic anhydride (16.2 g, 0.16 mole) was warmed during 3 h. Excess reagents were removed *in vacuo* and the residue was distilled at 10 mm, yielding 13.1 g. (83%) of the product, b.p. 135°. A sample redistilled at 2 mm, for analysis had b.p. 117–118°. Calc. for $C_7H_{11}NO_3$: N, 8.91. Found: N, 8.75%.

N - (*Trifluoroacetoxymethyl*)-*phthalimide.* A solution of *N* - (hydroxymethyl) - phthalimide (5.31 g, 0.03 mole), and trifluoroacetic acid (25 ml) in chloroform (50 ml) was refluxed during 4 h. The excess reagents were removed with the water pump, and the crude product was crystallized from ethylacetate to yield 2.7 g (50.8%) of recovered *N* - (hydroxymethyl) - phthalimide. Concentration of the mother liquor and addition of hexane gave 4 g, (48.8%) of *N* - (trifluoroacetoxymethyl) - phthalimide; m.p. 96–98° after recrystallization from ethylacetate–hexane. Calc. for $C_{11}H_{16}F_3NO_4$, N, 5.13. Found N, 5.62%.

N-(*Phthalimidomethyl*)-*acetamide.* This was prepared by the procedure given by Buc,[11] and also as follows: A solution of *N*-(hydroxymethyl)-phthalimide (8.85 g, 0.05 mole) and acetonitrile (10 ml) in trifluoroacetic acid (50 ml) was refluxed during 42 h. The reagents were removed with the water pump, and the crude product was crystallized from acetonitrile; yield 7.4 g (67.9%), m.p. 219–222°.

N-(*Phthalimidomethyl*)-n-*nonanamide* was prepared both by Buc's procedure (yield, 85.4%) and by the trifluoroacetic acid procedure described above (yield, 60.8%). The melting point, after crystallization from acetonitrile was 133–136°. Calc. for $C_{18}H_{24}N_2O_3$. N, 8.85; Found: N, 8.76%. The NMR spectrum of *N* - (phthalimidomethyl) - *n* - nonanamide was taken in $CDCl_3$ with tetramethylsilane as an internal standard: δ 0.85–1.2 (17 H), δ 2.2 (2H), δ 5.2 (2H), δ 6.6 (1H) and δ 7.8 (4H).

N - (2 - *Pyrrolidinonemethyl*) - n - *nonanamide* was prepared by a slight modification of Buc's procedure.[11] *N* - (Hydroxymethyl) - 2 - pyrrolidinone (5.75, 0.05 mole) and *n*-nonanenitrile (8.35 g, 0.06 mole) were mixed in concentrated sulfuric acid (30 ml), and the solution was left standing at room temperature for 1.5 h. The acid solution was poured into ice-water, and the resultant mixture was extracted with $CHCl_3$. After drying, the chloroform was removed *in vacuo*, and the crude residue was crystallized from acetonitrile, yielding 7.5 g, (59%) of the desired product; m.p. 75–78°. Calc. for $C_{14}H_{26}N_2O_2$: N, 11.01; Found: N, 10.77%.

Methylene-bis-phthalimide. A stirred mixture of potassium phthalimide (9.3 g, 0.05 mole) and methylene iodide (6.7 g, 0.025 mole) in *N,N*-dimethylformamide (200 ml) was maintained at 100° with magnetic stirring for 24 h. The solvent was removed *in vacuo*, and the crude product was crystallized from 2-propanol: chloroform; yield 4.6 g. (60%); m.p. 228–231°. Recrystallization from acetonitrile raised the m.p. to 230–234°.

Alkylations

The following procedure for the preparation of *N*-pentamethylbenzylphthalimide is typical. A solution of *N* - (hydroxymethyl) - phthalimide (5.31 g, 0.03 mole), pentamethylbenzene (4.45 g, 0.03 mole) and trifluoroacetic acid (25 ml) in

$CHCl_3$ (50 ml) was refluxed during 24 h. The solution was added to benzene (450 ml), and the benzene solution was washed with water, saturated sodium bicarbonate and water again. After drying over saturated magnesium sulfate, the benzene was removed *in vacuo*, and the crude product was crystallized from ethylacetate; yield 8.4 g. (91%); m.p. 183–186°.

Alkylation of pentamethylbenzene by N - (2 - *pyrrolidinonemethyl*) - n - *nonanamide.* A solution of *N* - (2 - pyrrolidinonemethyl) - *n* - nonanamide (2.54 g, 0.01 mole), pentamethylbenzene (1.63 g, 0.011 mole) and trifluoroacetic acid (10 ml) in $CHCl_3$ (20 ml) was refluxed during 50 hr. The solution was added to benzene (300 ml), and the benzene was washed with water (80 ml), saturated sodium bicarbonate (100 ml) and water (100 ml) again. The benzene solution was dried over anhydrous magnesium sulfate. The solvent was removed, and the residue was made up to a volume of 50 ml with chloroform. Analysis by GLC indicated the presence of 1.63 g (66.5%) of *N* - pentamethylbenzyl - 2 - pyrrolidinone and 0.26 g (8.2%) *N* - pentamethyl - benzyl - *n* - nonanamide. The analyses were done on a F&M model 720 dual column gas chromatograph with a thermal conductivity detector and helium as the carrier gas. A 6' column, packed with 10% SE-30 on 60–80 Diataport S and maintained isothermally at 270° was used. The *N* - pentamethylbenzyl - 2 - pyrrolidinone used in preparing the standard for analysis was obtained by alkylating pentamethylbenzene with *N* - (hydroxymethyl) - 2 - pyrrolidinone (Table 1), and the *N* - pentamethylbenzyl - *n* - nonanamide was prepared by the procedure given below.

N - *Pentamethylbenzyl* - n - *nonanamide.* A solution of pentamethylbenzylacetate (8.8 g, 0.04 mole), *n*-nonanenitrile (5.85 g, 0.042 mole) and trifluoroacetic acid (20 ml) in $CHCl_3$ was refluxed during 45 h. The solution was added to benzene (400 ml), and the benzene solution was washed with water, saturated sodium bicarbonate and again with water. After drying the benzene was removed, and the crude product was crystallized from hexane-chloroform to yield 8.8 g (69%) of product; m.p. 160–163°. Recrystallization from methanol raised the m.p. to 164–166°. Calc. for $C_{21}H_{35}NO$: N, 4.41; Found. N, 4.31%.

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