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THE QUESTION OF ANOMALIES IN THE FRIEDEL-CRAFTS ACYLATION OF HALOALKYLBENZENES

ACETYLATION OF THE ISOMERIC BROMO-*m*-XYLENES

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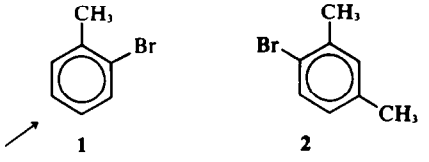
Abstract—The fact that Friedel-Crafts acylation in bromoalkylaromatics usually proceeds *para* to the bromine substituent has been considered to be an anomaly. The acetylation of the isomeric bromo-*m*-xylenes has been carried out, and product identification has confirmed this type of orientation. However, by a consideration of partial rate factors and competitive reactions, it is shown that these results may be quite acceptable.

In considering the electrophilic aromatic substitution of disubstituted benzenes, it has been generally accepted† that orientation is controlled by the most "activating" group. Hence, since toluene is much more reactive than bromobenzene in Friedel-Crafts acylation, the fact that *o*-bromotoluene, **1**, acetylates at the 5 position has been considered as an anomaly.[1] In fact, acylation *para* to the halogen in



1 **2**

haloalkylbenzenes has been noted as anomalous in two principal reviews.[1,2] In the earlier literature, a powerful "directing" effect of bromine was widely accepted, and it was reported[2,3] that 4-bromo-*m*-xylene, **2**, will not react with acetyl chloride and aluminum chloride because the position *para* to the bromine is blocked. The need to acylate compound **2** in connection with another study brought this problem to our attention, and we would now like to report our studies on the Friedel-Crafts acetylation of the three isomeric bromo-*m*-xylenes.

RESULTS AND DISCUSSION

For our own satisfaction we carried out the acetylation of **1**, and, in addition to obtaining a consistent NMR spectrum, oxidized it to a dicarboxylic acid. We found this material to be identical to the oxidation product of **2**, and thus, acetylation of **1** does in fact give substitution *para* to the bromine. However, contrary to the early report,[3] **2** did react with acetyl chloride and aluminum chloride in carbon disulfide to give 5 - bromo - 2, 4 - dimethyl - acetophenone, **3**, as the major product. When ethylene dichloride was used as the solvent, 2,4-dimethylacetophenone, **4**, and 4,6 - dibromo - *m*-xylene, **5**, were also detected, and the results are indicated in Table 1. The formation of **4** and **5** was initially thought due to prior disproportionation of **2** in the presence of $AlCl_3$[4] to give **5** and *m*-xylene which would be acetylated to **4**. However, for the reactions in $ClCH_2CH_2Cl$, the acetyl chloride/aluminum chloride complexes were carefully prepared separately in $ClCH_2CH_2Cl$, and, in some cases, filtered before dropwise addition to **2** in $ClCH_2CH_2Cl$. In order to determine the probability of disproportionation of **2** in the presence of complexed $AlCl_3$, a 1:1 complex of $AlCl_3$ and 2-pentanone was prepared in $ClCH_2CH_2Cl$ and added to a solution of one equivalent of **2** in $ClCH_2CH_2Cl$. Under these conditions, no *m*-xylene or 4,6 - dibromo - *m* - xylene were formed. Hence, we would suggest "ipso" attack[5] as an alternate explanation, which involves attack by the acetyl group at the 4-position followed by transfer of Br^+ to form **4** and **5**.

To further investigate the problem of orientation with bromo alkyl benzenes, we reacted 2-bromo-*m*-xylene, **6**, with acetyl chloride and aluminum chloride, and this resulted in essentially one product. The NMR spectrum showed a singlet in the aromatic region (2H), a singlet for the acetyl methyl (3H), and a singlet for the benzylic protons (6H). On this basis the product was determined to be 4 - bromo - 3, 5 - dimethylacetophenone, and acetyla-

†This concept is often presented in textbooks. See, for example, N. L. Allinger, M. P. Cava, D. C. DeJongh, C. R. Johnson, N. A. Lebel, C. L. Stevens, *Organic Chemistry* p. 369. Worth Publishers, New York (1971)

Table 1. Friedel-Crafts acetylation of 4-bromo-*m*-xylene, **2**

Solvent	Reaction Time	Yield, %[a] 3	4	5
$ClCH_2CH_2Cl$[b]	10 min	20		
$ClCH_2CH_2Cl$[b]	1 h	60	5%	5%
$ClCH_2CH_2Cl$[b]	24 h	75	5%	5%
CS_2[c]	24 h	61[d]		

[a] Yields based on VPC data, uncorrected for thermal conductivity factors; yields of **4** and **5** were somewhat variable.

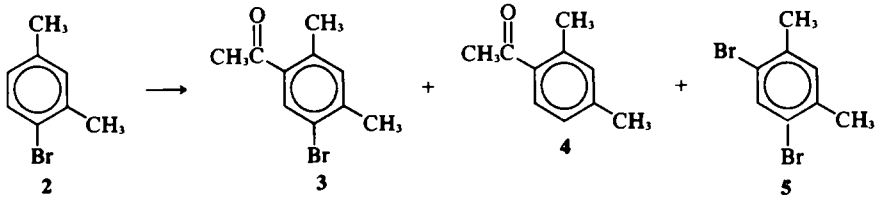
[b] A 1:1 $AlCl_3/CH_3COCl$ was prepared separately and added dropwise to **2** in $ClCH_2CH_2Cl$ at room temp.

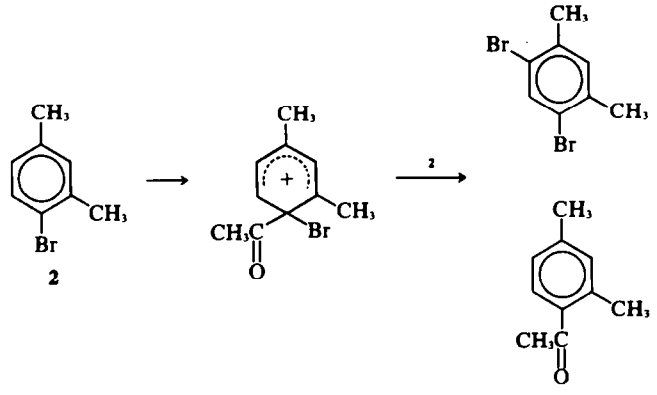
[c] Solid $AlCl_3$ was added to CH_3COCl and **2** in CS_2.

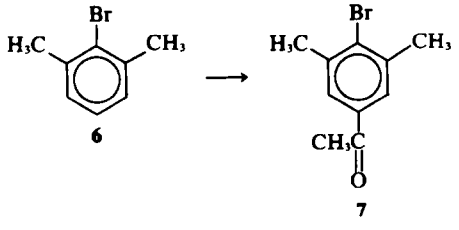
[d] Yield by isolation via distillation.

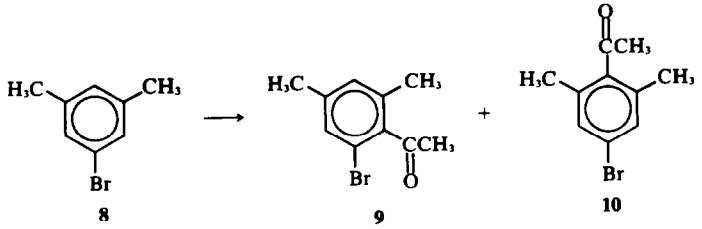
tion proceeded *para* to the bromine with little or no substitution *para* (and *ortho*) to the Me groups. Hence, the orientation for the Friedel-Crafts acetylation of **6** is controlled by the bromine in opposition to two Me groups. These results appear to be independent of solvent and temperature.

On the other hand, 5-bromo-*m*-xylene, **8**, reacts to give two products. Although complete resolution by GLPC was not achieved using several columns, a ratio of 2:1 was determined by the integrated areas of the acetyl Me groups in the NMR spectrum. The major product was isolated by chromatography on a column of silica gel, and showed two aromatic singlets, and three Me singlets in the NMR. Hence, it was assigned as structure **9**. By comparing this spectrum with the NMR









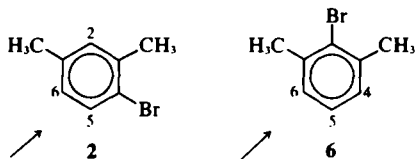
spectrum of the mixture, the spectrum of the minor product was determined to be an aromatic singlet (2H), a benzylic Me singlet (6H), and an acetyl Me (3H), and was concluded to correspond to structure **10**. Hence, there seems to be no "special" *para* directing effect from the bromine in the orientation of **8**.

In summary, our results indicate that there is no anomaly in the Friedel-Crafts acetylation of 4-bromo-*m*-xylene, **2**, (contrary to a very early report), although minor side products appear to be formed by "ipso" attack. Similarly, the 5-bromo isomer, **8**, does not give unexpected results with respect to orientation (i.e., no unusual *para* direction by bromine). The question that remains is why 2-bromo-*m*-xylene, **6**, and *o*-bromo-toluene, **1**, leads to products with orientation controlled by a "deactivating group" as opposed to one "activating" group in **1**, and two in **2**.

By using the partial rate factors for acetylation of toluene and bromobenzene,[6,7] the ratio of isomers can be estimated. From the data summarized in Table 2 one would "expect" attack *para* to the bromine in **1** as the predominant pathway. Since the value for attack at position 4 is overestimated,* almost exclusive formation of 4 - bromo - 3 - methylacetophenone would not be surprising on this basis. Similarly, the 5-position in compound **6** should account for almost half of the product. When the overestimate of m_f^{Br} is taken into account, together with expected steric effects, the exclusive acetylation at position 5 appears to be within reason.

*See footnote *c*, Table 2. The partial rate factors for the acylation of chlorobenzene are larger than bromobenzene. Since m_f^{Br} is unknown (too small to measure), m_f^{Cl} was used in its place as an upper limit.[7]

As a last point, we considered the possibility that a bromine adjacent to a methyl group somehow affects the group such that it no longer exerts its usual activating (orientating) effect. It appeared as though a competitive acetylation between **2** and **6** would afford any such information, since the 6-position in **2** is equivalent (for our considerations)



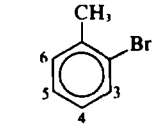
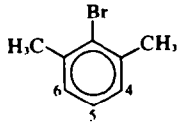
to the 4 (and 6) position in **6**. Hence, if the 4 and 6 positions of **6** are somehow less active because of the bromine adjacent to the methyls, then position 5 (where substitution occurs) should be less reactive than position 6 of **2**. In fact, when a mixture of **2** and **6** is reacted with $CH_3COCl/AlCl_3/ClCH_2CH_2Cl$, greater than 80% of the product is derived from **6**.

In conclusion, then, our results do not lend support to any particular anomaly in the systems which we have investigated. Thus, we feel that if there are any abnormalities in the Friedel-Crafts acylation of bromoalkylbenzenes, they are probably of a much smaller order of magnitude than previous considerations have suggested.

EXPERIMENTAL

Materials. The bromoxylene isomers **6** and **8** were obtained commercially. However, samples of isomer **2** from several commercial sources were all found to be ~10% impure (presumably contaminated with the 2-isomer). Thus, **2** was prepared by adding amyl nitrite dropwise to

Table 2. Partial rate factors for acetylation[a] of **1** and **6**

	Compound	Position of attack	Partial rate factors[b,c]	Calculated rates
1		4[d]	$p_f^{Me} \times m_f^{Br}$	2250×10^{-4}
		5[d]	$m_f^{Me} \times p_f^{Br}$	4132×10^{-4}
6		4 (and 6)	$p_f^{Me} \times o_f^{Me} \times 2 \times m_f^{Br}$	2·0
		5	$m_f^{Me} \times m_f^{Me} \times p_f^{Br}$	1·9

[a] For $CH_3COCl/AlCl_3/ClCH_2CH_2Cl$ acylations; *cf*, Ref 7.

[b] Where $o_f^{Me} = 4{\cdot}5$, $m_f^{Me} = 4{\cdot}8$, $p_f^{Me} = 750$ for toluene, and $p_f^{Br} = 0{\cdot}084$ and $m_f^{Br} \leq 0{\cdot}0003$ for bromobenzene.

[c] Since m_f^{Br} is now known, the value for m_f^{Cl} has been used in its place; presumably m_f^{Br} is significantly smaller.

[d] Values for ortho attack in **1** are negligible.

2,4-dimethylanilinium hydrobromide in refluxing carbon tetrachloride.[8]

Friedel-Crafts acetylations. These reactions were carried out by two methods. *Method A.* Aluminum chloride was added to acetyl chloride in ethylene dichloride at room temp* (unless otherwise indicated), and this mixture was stirred for 10 min to insure complex formation. This soln was then decanted (or filtered) into a dropping funnel, and added dropwise to a stirred soln of the bromoxylene in ethylene dichloride. After the desired length of time, the mixture was poured into cold dil HCl. The organic layer was washed with water and dilute base as usual, and then dried and evaporated. *Method B.* Solid aluminum chloride was added (in parts) to a stirred soln of the bromoxylene in CS_2. After the desired length of time, the mixture was poured into cold dil HCl and worked up as indicated above.

5-Bromo-2,4-dimethylacetophenone. 4-Bromo-*m*-xylene (12 g, 65 mmol) in cold CS_2 (75 ml) was reacted with acetyl chloride (6·1 g, 1·2 equiv) and $AlCl_3$ (12·1 g, 1·4 equiv) according to method A. After 30 min, the ice bath was removed and stirring continued for 4 h. At this point gas evolution was still observed, and the reaction was stirred overnight. Workup gave a brown oil which was distilled through a Vigreaux column (b.p. 117°, 3 mm) to give an oil (8·9 g, 61%) which crystallized on standing. NMR (CCl_4): aromatics δ 7·75 (s, 1H), 7·0 (s, 1); acetyl Me 2·49 (s, 3); benzylic methyls 2·38 (s, 3) and 2·33 (s, 3). (Found: C, 52·64; H, 4·81; Br, 35·25. Calcd for $C_{10}H_{11}OBr$: C, 52·89; H, 4·88; Br, 35·18%). 4-Bromo-*m*-xylene was also reacted according to method B, and the data was summarized in Table 1. The side products 2,4-dimethylacetophenone and 4,6 - dibromo - *m* - xylene were trapped from the gas chromatograph, and identified by mass spectral analysis and comparison of the NMR with known spectra.

4 - Bromo - 3,5 - dimethylacetophenone. 2 - Bromo - *m*-xylene (1·2 g, 6·5 mmol) in ethylene dichloride (15 ml) was reacted with acetyl chloride (0·5 g, 1 equiv) and $AlCl_3$ (0·87 g, 1 equiv) according to method B. Quenching after 3 h resulted in a 40% yield (by integration of the NMR peaks), and an analytical sample was isolated by chromatography on silica gel. NMR (CCl_4): aromatics δ 7·5 (s, 2H); acetyl Me, 2·47 (s, 3); benzylic methyls, 2·45 (s, 6). (Found: C, 52·69; H, 4·85; Br, 34·95. Calcd for $C_{10}H_{11}OBr$: C, 52·89; H, 4·88; Br, 35·18%). Under several reaction conditions (including increased reaction times and elevated temps), substantial amounts of a product were obtained which showed an AB pattern in the aromatic region of the NMR. However, when the reaction was run under our usual conditions for method B with the rigorous exclusion of free $AlCl_3$, this product did not appear and was not investigated further.

6 - Bromo - 2, 4 - dimethyl and 4 - bromo - 2, 6 - dimethylacetophenone. 5-Bromo-*m*-xylene (8·0 g, 43·5 mmol) in ethylene dichloride (30 ml) was reacted with acetyl chloride (3·9 g, 1·2 equiv) and $AlCl_3$ (6·9 g, 1·2 equiv) according to method B. The reaction was allowed to stir overnight, and resulted in a 60% yield of acylated products (by integration of the NMT peaks).† The product was distilled through a Vigreaux column and the final fractions (b.p. 150–153°, water aspirator) proved to be a mixture of 6-bromo-2,4-dimethyl and 4-bromo-2, 6 - dimethylacetophenone (2:1). These two products could not be separated using several GLPC columns, and the analysis given corresponds to the mixture of both isomers. NMR (CCl_4): aromatics δ 7·1, 6·9; acetyl methyls 2·4, 2·3; benzyl methyls 2·2, 2·1. (Found: C, 53·00; H, 4·95; Br, 34·98. Calcd for $C_{10}H_{11}OBr$: C, 52·89; H, 4·88; Br, 35·18%).

Curiously, the major isomer, **9**, was once isolated by chromatography on silica gel, but this could not be repeated. Its NMR was determined as follows: aromatics δ 7·1 (s, 1H), 6·9 (s, 1); acetyl Me 2·4 (s, 1); benzyl methyls 2·2 (s, 3) and 2·1 (s, 3). Hence, the NMR spectrum of 1° is deduced to be aromatics δ 7·1 (s, 2H); acetyl methyl 2·3 (s, 3); benzyl methyls 2·1 (s, 6H), which indicates that two of these three singlets overlap exactly with signals of isomer **9**.

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*Ca. 25°. The reactions of Ref 6 were run at 25·0°C.

†Smaller scale reactions with 1·3 equiv each of acetyl chloride and aluminum chloride gave somewhat better yields (~85%).

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