Haloarenes in the Duff reaction under high pressures
2.* Formylation and amidomethylation of haloarenes in trifluoroacetic acid

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Reactions of haloarenes with urotropine in CF_3COOH at elevated temperatures and high pressures give the corresponding aromatic aldehydes and/or *N*-(haloarylmethyl)trifluoroacetamides. The yeilds of the products and their ratio depend on electronic properties of substituents in the aromatic ring. The reaction carried out in a mixture of CF_3COOH and $(CF_3CO)_2O$ affords only amides.

Key words: haloarenes, Duff reaction, high pressure, haloarenecarbaldehydes, *N*-(haloarylmethyl)trifluoroacetamides.

Interaction of urotropine (hexamethylenetetramine, HMTA) with relatively active aromatic compounds (alkylbenzenes, derivatives of phenols or anilines, *etc.*) in a protonic acid medium yields the corresponding aldehydes after hydrolysis of the reaction mixture (the Duff reaction). We were first to demonstrate[2] that even relatively deactivated compounds such as halobenzenes can react with HMTA if the process is carried out at high pressures (*P*) and high temperatures (*T*) in trifluoroacetic acid (TFAA) (method 1). Depending on the nature of the aryl halide, the reaction yields both the normal products of the Duff reaction, isomers of aromatic aldehydes (**2a—e**), and *N*-(haloarylmethyl)trifluoroacetamides (**3a—c**, **f—h**) as mixtures of isomers or a single isomer (**3i**) (Scheme 1).

The substantially more inert dihalobenzenes, *para*-dichlorobenzene (**1j**) and *para*-dibromobenzene (**1k**), react with HMTA only when a mixture of TFAA with its anhydride is employed (method 2).

Yields of the resulting compounds and the ratios between isomers are presented in Table 1. Despite the fact that isolation of the products is accompanied by some losses, these data make it possible to discuss the influence of substituents on the reactivities of the starting aromatic compounds.

Since formylation involves electrophiles with moderate reactivities,[3] electronic properties of the substituents in the substrate molecules are of prime importance. From data listed in Table 1, one can see that relative increase in the electron density at the reaction center caused by substituents results in both an increase in the proportion of aldehydes in the products of the reaction carried out by method 1 and a decrease in the temperature necessary for the process. For example, the reaction of **1a** at 90 °C according to method 1 yields almost exclusively aldehydes, and reaction of **1c** at 120 °C affords mainly amides, which is obviously governed by the variation of the properties of substituents from noticeably electron-donating (F) to weakly pronounced electron-withdrawing (Br) properties (based on the σ^+ values).[4] Previously we obtained similar data on the effects of halogens in the ring of aromatic aldehydes on the Henry reaction.[5]

When HMTA reacts with *meta*-bromotoluene (**1e**) (coincident directing effects of the substituents), mostly aldehydes are formed, and the reaction with its *para*-isomer (**1f**) (noncoincident directing effects), gives only amides.

In the case of 1-chloronaphthalene (**1d**), 5-chloro-1-naphthaldehyde (**2d**) is produced. Note that chlorination of 1-naphthaldehyde yields the same product.[6]

From dihalobenzenes, only the corresponding amidomethyl derivatives have been synthesized. However, it is difficult to explain, why the use of method 1 is sufficient to introduce compounds **1g—i** into the reaction, while for the reaction of **1j,k** to proceed, the much more drastic conditions of method 2 are required.

As can be seen from Table 1, method 2 can be used for directed preparation of amides **3**, including those haloarenes, which yield greater or smaller quantities of aldehydes when react according to method 1.

Attention is attracted by the higher selectivity of formylation of halobenzenes compared to amidomethylation. The reactivity of fluorobenzene in this process substantially stands out. In fact, its reaction according to method 1 affords 8.5 % *ortho*-isomer in a

* For Part 1, see Ref. 1.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 11, pp. 2221—2224, November, 1995.
1066-5285/95/4411-2127$12.50

Scheme 1

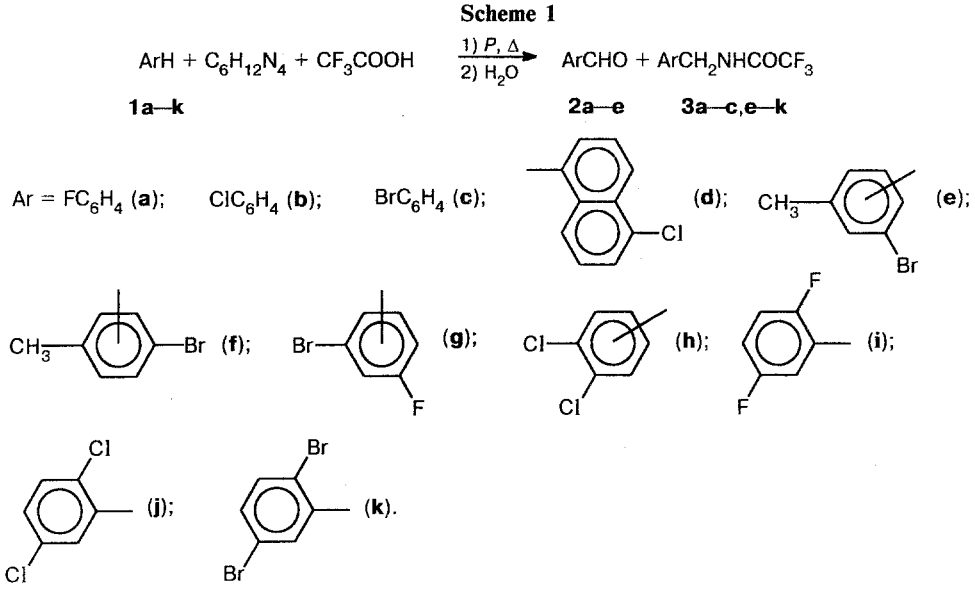


Table 1. Data on formylation and amidomethylation of haloarenes (500 MPa, 9 h)

Arene	Method[a]	*T*/°C	Recovered **1**[b] (%)	Yield of **2** (%)	Ratio[c] between the isomers **2** *para*/*ortho* (%)	Yield of **3** (%)	Ratio[c] between the isomers **3** *para*/*ortho* (%)
1a	1	90	30	56	91.5/8.5	—[d]	67.6/32.4
1a	2	100	—[e]	0	—	46	94.7/5.3
1a	3	100	—	0	—	—[e]	61.6/38.4
1b	1	120	31	31	65.8/34.2	25	54.6/45.4
1c	1	120	18	24	59.7/40.3	28	52.8/47.2
1c	3	120	—	0	—	—[e]	50.8/49.2
1d[f]	1	90	22	63	—[g]	0	—
1e	1	120	—	48	—[h]	—[d]	—[e]
1f	1	120	48	0	—	39	[i]
1g	1	140	—	0	—	37	—[e]
1h	1	140	—	0	—	35	[j]
1i	1	140	—	0	—	62	[g]
1j	2	200	—	0	—	38	[g]
1k	2	200	—	0	—	58	[g]

[a] Method 1 involves reaction of **1** with HMTA in TFAA; method 2 involves reaction of **1** with HMTA in TFAA mixed with its anhydride; method 3 is reaction of **1** with *N*,*N*′-bis(trifluoroacetyl)methanediamine (**4**) in TFAA. [b] Found by GLC. [c] Determined for reaction mixtures by GLC-MS. [d] The yield of nonisolated product was <15 %. [e] Not determined. [f] Duration of the reaction was 15 h (with twofold dilution of the mixture with TFAA). [g] One isomer. [h] Ar = 2-Br-4-MeC_6H_3 (70.7 %), Ar = 4-Br-2-MeC_6H_3 (26.3 %), Ar = 2-Br-6-MeC_6H_3 (3.1 %). [i] Ar = 2-Br-5-MeC_6H_3 (67.2 %), Ar = 5-Br-2-MeC_6H_3 (32.8 %). [j] Ar = 3,4-$Cl_2C_6H_3$ (68.3 %), Ar = 2,3-$Cl_2C_6H_3$ (31.7 %).

mixture of aldehydes and 32.4 % *ortho*-isomer in a mixture of amides, whereas in the case of bromobenzene (**1c**) these values are 40.3 % and 47.2 %, respectively.

In the case of bromotoluenes, *ortho*-substitution with respect to Br proved to be preferable for both compound **1e** (*ortho*- and *para*-substitution is possible under coincident directing effects of the substituents) and compound **1f** (*ortho*- and *meta*-substitution is possible under noncoincident directing effects of the substituents).

In the reaction products obtained from compound **1h**, *N*-(3,4-dichlorophenylmethyl)trifluoroacetamide predominates, probably due to steric reasons.

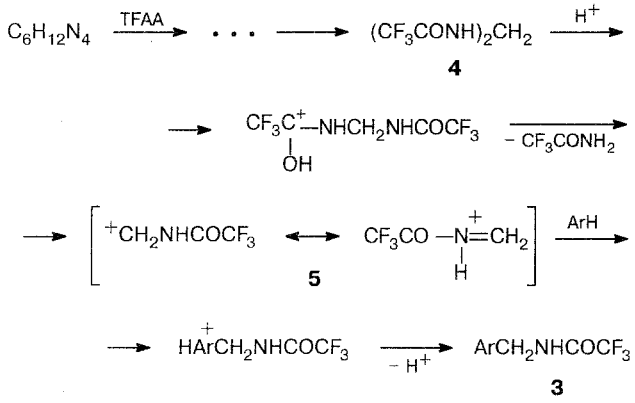
A GLC-MS analysis of reaction mixtures indicates that, along with aromatic compounds, products of acidic degradation of HMTA (up to trifluoroacetamide and its *N*-methyl derivative), specifically, *N*,*N*′-bis-(trifluoroacetyl)methanediamine (**4**), are formed.

When diamine **4** was introduced into the reactions with **1a**,**c** instead of HMTA (method 3, Table 1), only

the corresponding amides were obtained, which allows compound **4** to be regarded as an intermediate in amidomethylation of arenes by HMTA. This conclusion is confirmed by the fact that the ratios between *ortho*- and *para*-isomers of amides **3a,c** synthesized by methods 1 and 3 are similar.

Thus, one may suggest that the formation of amides **3** in the reactions of arenes with HMTA in a TFAA medium occurs both *via* the same intermediate as the formation of aldehydes, *viz.*, arylmethylamine (*cf.* the generally accepted scheme of the formation of aldehydes in the Duff reaction[7]), and by an independent pathway (according to Scheme 2), contributions of these two pathways depending on the reaction conditions and the nature of the arene.

Scheme 2



Cation **5** is appreciably destabilized by the trifluoroacetyl group, which could account for the lower regioselectivity of amidomethylation compared to formylation.

Experimental

Melting points were determined using a Kofler hot-stage apparatus. ^{1}H NMR spectra were recorded on Bruker WM-250 and Jeol-90 FQ spectrometers using HMDS as the internal standard (δ = 0.055). Qualitative analysis of reaction mixtures was carried out on a Finnigan MAT INCOS-50 quadrupole GLC-MS spectrometer (EI, 70 eV, a 0.25 mm × 30 m capillary column with 0.25 μ polydimethylsiloxane as a grafted phase). Quantitative analysis was carried out on a Biokhrom 1M GL chromatograph (a 2 mm × 3 m glass column, 0.16—0.20 mm Chromaton N-AW DMCS as the support and 5 % XE 60 as the phase). Normal hydrocarbons served as reference compounds for calibration.

The reactions were carried out in Teflon ampules in high-pressure setups with an effective volume of more than 100 cm^3.[8]

Reactions of haloarenes with HMTA. Method 1. Haloarene (50 mmol), HMTA (50 mmol), and TFAA (885 mmol) were placed into a Teflon ampule, and the mixture was kept for 9 h at the desired temperature under a pressure of 500 MPa. Excess TFAA was evaporated, and the mixture was neutralized by a solution of K_2CO_3 and extracted with ether (3×(50 to 100 mL)). The combined extracts were washed with dilute HCl and concentrated to 50—100 mL. The concentrated mixture was treated with a saturated solution of $NaHSO_3$ (2×100 mL) for 2—3 h. The bisulfite derivative was isolated, washed with ether, and decomposed with HCl. Aldehydes **2** were isolated by extraction with ether followed by its evaporation.

The concentrated ethereal solution remaining after isolation of aldehydes was applied onto 40×60 μ silica gel, eluted with a hexane—ether (2:1) mixture to give amides **3**. In some syntheses, diamide **4** was isolated by further elution with a hexane—ether (1 : 1) mixture.

Method 2. The reaction between haloarene (10 mmol), HMTA (10 mmol), TFAA (88 mmol), and trifluoroacetic anhydride (48 mmol) was carried out according to method 1, and amides **3** were isolated in a similar way (in some cases, diamide **4** was also isolated).

The yields of reaction products are listed in Table 1.

Data on the reaction of HMTA with fluorobenzene (**1a**) were reported in Ref. 1.

2-Chloro- and 4-chlorobenzaldehydes (2b) were isolated as an oil (the ratio between the *para*- and *ortho*-isomers was 80 : 20 (^{1}H NMR)). The products were identified by the retention times in GLC.

***N*-(2-Chlorophenylmethyl)- and *N*-(4-chlorophenylmethyl)trifluoroacetamides (3b)** were isolated as crystals (R_f ~0.4), with the *para*-to-*ortho* ratio being 60 : 40 (^{1}H NMR). Twofold recrystallization of **3b** from hexane afforded 1.35 g (11.4 %) of the *para*-isomer, m.p. 91—92.5 °C. Found (%): C, 45.61; H, 2.97; F, 24.07; N, 5.91. $C_9H_7ClF_3NO$. Calculated (%): C, 45.49; H, 2.97; F, 23.99; N, 5.90. MS, *m/z*: 237 [M]$^+$. ^{1}H NMR ($CDCl_3$), δ: 4.47 (d, 2 H, CH_2); 6.8—7.1 (br.s, 1 H, NH); 7.21 (d, 2 H, Ar); 7.33 (d, 2 H, Ar).

2-Bromo- and 4-bromobenzaldehydes (2c) were obtained by method 1 as an oil, with the *para*-to-*ortho* ratio being 70 : 30 (^{1}H NMR). The products were identified by the retention times in GLC.

***N*-(2-Bromophenylmethyl)- and *N*-(4-bromophenylmethyl)trifluoroacetamides (3c)** were obtained by method 1 as crystals (R_f ~0.4), with the *para*-to-*ortho* ratio being 50 : 50 (^{1}H NMR). Similarly to **3b**, 1.71 g (12.1 %) of the *para*-isomer was isolated, m.p. 116—117 °C. Found (%): C, 38.49; H, 2.50; F, 20.21; N, 4.90. $C_9H_7BrF_3NO$. Calculated (%): C, 38.32; H, 2.42; F, 20.21; N, 4.97. MS, *m/z*: 283 [M]$^+$. ^{1}H NMR (acetone-d_6), δ: 4.50 (d, 2 H, CH_2); 7.31 (d, 2 H, Ar); 7.53 (d, 2 H, Ar); 8.8—9.1 (br.s, 1 H, NH).

5-Chloro-1-naphthaldehyde (2d) was obtained as an oil using method 1 (15 h) with twofold dilution of the mixture with TFAA (due to low solubility of the starting **1d**), m.p. of the semicarbazone 236—238 °C (Ref. 4: 239 °C). MS, *m/z*: 191 [M]$^+$. ^{1}H NMR ($CDCl_3$), δ: 7.6—7.9 (m, 4 H, Ar); 8.37 (m, 1 H, Ar); 9.27 (m, 1 H, Ar); 10.33 (s, 1 H, CHO).

2-Bromo-4-methyl- and 4-bromo-2-methylbenzaldehydes (2e) were isolated as an oil. The signals recorded for the isomer mixture were assigned as follows: (1) the ^{1}H NMR spectrum of the *2-bromo-4-methyl isomer* (70 %) ($CDCl_3$), δ: 2.40 (s, 3 H, Me), 7.21 (d, 1 H, Ar), 7.45 (s, 1 H, Ar), 7.80 (d, 1 H, Ar), 10.30 (s, 1 H, CHO); (2) the ^{1}H NMR spectrum of the *4-bromo-2-methyl isomer* (30 %) ($CDCl_3$), δ: 2.65 (s, 2 H, Me); 7.40—7.55 (m, 2 H, Ar); 7.66 (d, 1 H, Ar); 10.20 (s, 1 H, CHO). MS, *m/z*: 201 [M]$^+$.

***N*-(2-Bromo-5-methylphenylmethyl)- and *N*-(5-bromo-2-methylphenylmethyl)trifluoroacetamides (3f).** The isomers were separated by repeated chromatography using a hexane—ether (4 : 1) mixture as an eluent.

2-Bromo-5-methyl isomer, R_f = 0.40. Yield 21 %, m.p. 74—78 °C (from hexane). Found (%): C, 40.44; H, 3.07; F, 19.20; N, 4.62. $C_{10}H_9BrF_3NO$. Calculated (%): C, 40.54; H, 3.06; F, 19.26; N, 4.73. ^{1}H NMR ($CDCl_3$) δ: 2.32 (s, 3 H, Me); 4.56 (d, 2 H, CH_2); 6.7—7.0 (br.s, 1 H, NH); 7.04 (d, 1 H, Ar); 7.20 (s, 1 H, Ar); 7.46 (d, 1 H, Ar).

5-Bromo-2-methyl isomer, R_f = 0.30. Yield 10 %, m.p. 89—92 °C (from hexane). Found (%): C, 40.61; H, 3.10; F, 19.38; N, 4.79. $C_{10}H_9BrF_3NO$. Calculated (%): C, 40.54; H, 3.06; F, 19.26; N, 4.73. ^{1}H NMR ($CDCl_3$), δ: 2.28 (s, 3 H, Me); 4.60 (d, 2 H, CH_2); 6.3—6.7 (br.s, 1 H, NH); 7.10 (d, 1 H, Ar); 7.35—7.40 (m, 2 H, Ar). MS, *m/z*: 297 $[M]^+$.

***N*-(2-Bromo-4-fluoro-, 4-bromo-2-fluoro-, and 2-bromo-6-fluorophenylmethyl)trifluoroacetamides (3g)** were isolated as an oil that slowly crystallized during storage. The signals recorded for the isomer mixture were assigned as follows: (1) the ^{1}H NMR spectrum of the *2-bromo-4-fluoro isomer* (70 %) ($CDCl_3$), δ: 4.49 (d, 2 H, CH_2), 7.1 (m, 3 H, Ar), 7.5—7.8 (br.s, 1 H, NH); (2) the ^{1}H NMR spectrum of the *4-bromo-2-fluoro isomer* (20 %) ($CDCl_3$) δ: 4.45 (d, 2 H, CH_2), 6.95 (m, 3 H, Ar), 7.8—8.0 (br.s, 1 H, NH); (3) for the *2-bromo-6-fluoro isomer* (10 %), only a signal at 4.65 ppm (d, 2 H, CH_2) can be assigned, while signals corresponding to the remaining protons are covered by signals of other isomers. MS, *m/z*: 300 $[M]^+$.

***N*-(2,3-Dichlorophenylmethyl)- and *N*-(3,4-dichlorophenylmethyl)trifluoroacetamides (3h)** were obtained as crystals (R_f ~0.4) containing ~25 % of the 2,3-dichloro isomer (^{1}H NMR). Similarly to **3b**, 2.23 g (16 %) of *N*-(3,4-dichlorophenylmethyl)trifluoroacetamide was isolated, m.p. 71—72.5 °C. Found (%): C, 39.84; H, 2.50; F, 21.32; N, 5.14. $C_9H_6Cl_2F_3NO$. Calculated (%): C, 39.73; H, 2.22; F, 20.95; N, 5.15. MS, *m/z*: 271 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ: 4.45 (d, 2 H, CH_2); 7.10 and 7.05—7.20 (d and br.s, 2 H, Ar and NH); 7.35 (s, 1 H, Ar); 7.41 (d, 1 H, Ar).

***N*-(2,5-Difluorophenylmethyl)trifluoroacetamide (3i)** (R_f = 0.40), m.p. 82.5—84.0 °C (from hexane). Found (%): C, 45.45; H, 2.58; F, 38.74; N, 5.95. $C_9H_6F_5NO$. Calculated (%): C, 45.20; H, 2.53; F, 39.72; N, 5.86. MS, *m/z*: 239 $[M]^+$. ^{1}H NMR (acetone-d_6), δ: 4.60 (d, 2 H, CH_2); 7.15 (m, 3 H, Ar); 8.8—9.1 (br.s, 1 H, NH).

***N*-(2,5-Dichlorophenylmethyl)trifluoroacetamide (3j)** (R_f = 0.45), m.p. 93—95.0 °C (from hexane). Found (%): C, 39.94; H, 2.17; F, 20.66; N, 5.11. $C_9H_6Cl_2F_3NO$. Calculated (%): C, 39.73; H, 2.22; F, 20.95; N, 5.15. MS, *m/z*: 271 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ: 4.60 (d, 2 H, CH_2); 6.6—6.9 (br.s, 1 H, NH); 7.30 (m, 3 H, Ar).

***N*-(2,5-Dibromophenylmethyl)trifluoroacetamide (3k)** (R_f = 0.45), m.p. 113.5—116 °C (benzene—hexane). Found (%): C, 30.06; H, 1.63; F, 15.70; N, 3.88. $C_9H_6Br_2F_3NO$. Calculated (%): C, 29.94; H, 1.68; F, 15.79; N, 3.88. MS, *m/z*: 361 $[M]^+$. ^{1}H NMR (acetone-d_6) δ: 4.60 (d, 2 H, CH_2); 7.5 (m, 3 H, Ar); 9.0—9.3 (br.s, 1 H, NH).

***N,N'*-Bis(trifluoroacetyl)methanediamine (4).** Compound **4** was isolated from the products of the reaction of **1i** with HMTA, (R_f = 0.2), yield 17.4 %, sublimation temp. >180 °C. Found (%): C, 25.12; H, 1.71; F, 48.00; N, 11.64. $C_5H_4F_6N_2O_2$. Calculated (%): C, 25.22; H, 1.69; F, 47.88; N, 11.78. MS, *m/z*: 238 $[M]^+$. ^{1}H NMR (acetone-d_6), δ: 4.99 (t, 2 H, CH_2); 9.0—9.3 (br.s, 2 H, NH)

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Received June 17, 1994;
in revised form June 15, 1995