A novel synthesis of chloroacetamide derivatives via *C*-amidoalkylation of aromatics by 2-chloro-*N*-(2,2,2-trichloro-1-hydroxyethyl)acetamide

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Dedicated to Professor Usein M. Dzhemilev on the occasion of his 65th anniversary

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Abstract

A synthetic approach to the preparation of novel 2-chloro-*N*-(2,2,2-trichloro-1-arylethyl)acetamides on the basis of *C*-amidoalkylation of aromatics with 2-chloro-*N*-(2,2,2-trichloro-1-hydroxyethyl)acetamide has been developed. Scope and limitations of the synthesis of new chloroacetamide derivatives were demonstrated.

Keywords: Chloroacetamide, hemiaminals, chloral, *C*-amidoalkylation, aromatics

Introduction

C-Amidoalkylation[1] is a significant synthetic method for the preparation of various functionalized amide derivatives which are widely used as key reagents in the synthesis of important compounds: aminoaldehydes and aminoketones,[2] aminoacids,[3] amidines,[4] carbamides,[5] indene derivatives,[6] heterocycles,[7] including analogues of natural substances.[8]

N-(2,2,2-Trichloro-1-hydroxyethyl)amides are available amidoalkylating reagents which can be synthesized easily from chloral or chloralhydrate and various amides.[1,9] Halogen-containing hemiaminals are applied for synthesis of heterocyclic compounds.[10] They were used also in the earlier works[11] in *C*-amidoalkylation of aromatics. A range of aromatic compounds was involved in reactions with *N*-(2,2,2-tribromo-1-hydroxyethyl)benzamide, *N*-(2,2,2-trichloro-1-hydroxyethyl)acetamide, -trichloroacetamide, -acrylamide, -benzamides and -urethanes in the presence of concentrated sulfuric acid to produce corresponding *N*-(2,2,2-trihalo-1-arylethyl)amides in 20-88% yield. The products of amidoalkylation were used in subsequent synthesis of haloalkylamides, dichlorovinylamides, imines, hydroxyacides, aminoacides.[11] However, derivatives of monochloroacetamide were not studied in these reactions.

In continuation of our interest on chemistry of functionalized chloroacetamide derivatives,[12] we studied *C*-amidoalkylation of aromatics by 2-chloro-*N*-(2,2,2-trichloro-1-hydroxyethyl)acetamide **1** (Scheme 1) in order to develop a convenient way to promising biologically active compounds and reagents for heterocyclic chemistry.

Because of the high mobility of chlorine atom and reactive N-H group, compounds containing chloroacetamide moiety are known to be useful synthetic scaffolds for design of aziridines,[13] lactams,[14] piperazines,[15] oxazolidines,[16] imidazolidines and tetrahydropyrimidines – precursors of heterocyclic carbenes,[17] macrocyclic ligands,[18] dendrimers.[19] 2-Chloracetamide derivatives found application in solid-state chemistry,[20] in synthesis of aminoacids,[21] natural compounds[22] and their homologs,[23] pharmacologically promising substances[24] and biomarkers,[25] reagents for polymer modification,[26] ion-exchange resins for heavy and radioactive metal sorption.[27] Chloroacetamide pesticides[28] and dyes[29] are also well known. Thus, investigation of 2-chloroacetamide chemistry is an actual task both from theoretical and applied viewpoints.

Results and Discussion

As preliminary investigation, a range of Lewis and Bronsted acids was screened as catalysts in the model reaction of hemiaminal **1** with toluene (Table 1).

Table 1. The Screening of Lewis and Bronsted Acids for *C*-amidoalkylation of toluene by 2-chloro-*N*-(2,2,2-trichloro-1-hydroxyethyl)acetamide **1**

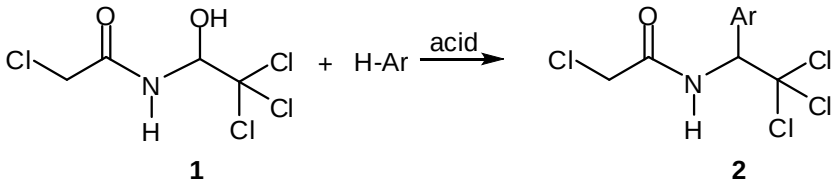
Entry	Amounts of **1** : toluene	Catalyst (amount)	Time, h	Temperature	Yield of **2a**, %
1	10 mmol : 10 mmol[a]	-	24	rt	0
2	10 mmol : 10 mmol[a]	BF_3 etherate (2 mmol)	24	rt	0
3	10 mmol : 10 mmol[a]	$ZnCl_2$ (2 mmol)	24	rt	0
4	10 mmol : 10 mmol[a]	$AlCl_3$ (2 mmol)	24	rt	8
5	10 mmol : 10 mmol[a]	P_4O_{10} (2 mmol)	24	rt	10
6	10 mmol : 10 mmol[a]	TfOH (2 mmol)	24	rt	18
7	10 mmol : 10 mmol[a]	H_2SO_4 (2 mmol)[b]	5	rt	52
8	10 mmol : 10 mmol[a]	oleum[c] (0.20 g)	5	rt	58
9	10 mmol : 10 mmol[a]	H_2SO_4 (2 mmol)[b] P_4O_{10} (2 mmol)	5	rt	65
10	10 mmol : 10 mmol[a]	H_2SO_4 (5 mmol)[b] P_4O_{10} (5 mmol)	3	rt	78
11	10 mmol : 30 mmol	H_2SO_4 (10 mmol)[b] P_4O_{10} (5 mmol)	2.5	rt	92
12	10 mmol : 30 mmol	H_2SO_4 (10 mmol)[b] P_4O_{10} (5 mmol)	2.5	40 °C	38

[a]CCl_4 (5 mL) was used as a diluent. [b]H_2SO_4 96% was used in the reaction. [c]Oleum 12% free SO_3 was used.

The formation of 2-chloro-*N*-[2,2,2-trichloro-1-(4-methylphenyl)ethyl]acetamide **2a** was found to proceed smoothly in the presence of strong Bronsted acids (Entry 5-11). When we used BF_3 etherate and $ZnCl_2$ or in the absence of a catalyst (Entry 1-3) no reaction took place. For $AlCl_3$ (Entry 4) *C*-amidoalkylated toluene derivative **2a** was produced after a long period in poor yield. The highest yield was achieved for the mixture of H_2SO_4 with P_4O_{10} (Entry 9-11). Moreover, excess of toluene had a beneficial effect on the reaction.

It was ascertained for different aromatic structures that *C*-amidoalkylation also occurred with benzene, phenol, anisole, naphthalene and 2-chlorothiophene (Table 2). Accordingly, mono substituted aromatics containing electron-donating groups, annulated aromatics and non-acidophobic electron-enriched heteroaromatics can be used in the synthesis of 2-chloroacetamide derivatives of the type **2** by *C*-amidoalkylation with hemiaminal **1**.

Authors, please redraw the Scheme 1 in ChemDraw or ISISDraw and send it to us as cdx or skc file. Thank you



1 **2**

Scheme 1. *C*-Amidoalkylation of aromatics with hemiaminal **1**.

Table 2. Hemiaminal **1** in *C*-amidoalkylation of aromatics in the presence of H_2SO_4 – P_4O_{10} mixture (see Scheme 1)

Entry	Ar	**2**	Time, h	mp, °C	Yield of **2,** %
1	4-MeC_6H_4	**2a**	2.5	122-123	92
2	Ph **()**	**2b**	3	130-131	87
3	4-HOC_6H_4	**2c**	2.5	115-116	81
4	4-$MeOC_6H_4$	**2d**	2.5	85-86	92
5	1-naphthyl	**2e**	5	137-140	89
6	5-chlorothien-2-yl	**2f**	4	127-128	85

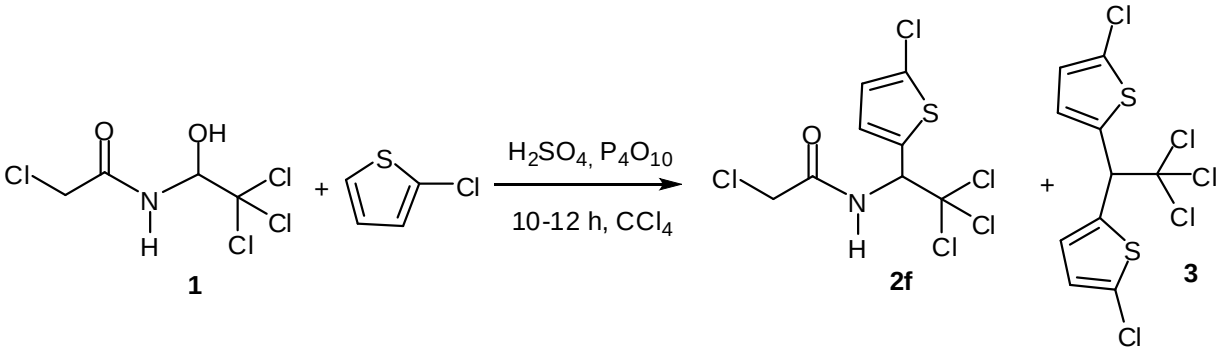
In the earlier works[11] devoted to *C*-amidoalkylation of aromatics by *N*-(2,2,2-trichloro-1-hydroxyethyl)amides a large excess of sulfuric acid (2–20 equivalents) was used for activation of the process. The reaction time took 50–100 h. In the present paper, we found that under action of H_2SO_4 – P_4O_{10} mixture the reaction proceeded for 2.5–5 h (Table 2). Unfortunately, under the conditions studied halobenzenes, aromatics, containing electron-withdrawing substituents, and disubstituted aromatics did not react with hemiaminal **1**. The results suggest that hemiaminal **1** possesses similar *C*-amidoalkylating activity in comparison to *N*-(2,2,2-trichloro-1-hydroxyethyl)sulfonamides studied in our earlier works.[30]

The experimental data obtained allowed one to reach the conclusion that the reaction of aromatics with hemiaminal **1** depends on electronic effect of a substituent in an aromatic ring. So,

the *C*-amidoalkylation proceeded in a selective manner to produce only *para*-substituted derivatives without admixtures of *ortho*- or *meta*-substituted isomers.

It should be noted that heating of reaction mass or increase of reaction time resulted in lower yield (see Table 1, Entry 12) probably due to side processes (sulfonation, acidolysis, resinification). In the case of 2-chlorothiophene when we increased the reaction period over 10 h the formation of minor 2,2′-(2,2,2-trichloroethane-1,1-diyl)bis-(5-chlorothiophene) **3** as admixture took place (Scheme 2). It is likely that amide **2f** acted as *C*-alkylating reagent and chloroacetamide moiety fulfilled the role of a leaving group. We noted earlier[31] that compound **3** could result from *C*-amidoalkylation of 2-chlorothiophene with *N*-(2,2,2-trichloro-1-hydroxyethyl)-2-thiophenesulfonamide in the same manner.

Authors, please redraw the Scheme 2 in ChemDraw or ISISDraw and send it to us as cdx or skc file. Thank you



Scheme 2. Formation of the side product **3**.

The structure of *C*-amidoalkylated aromatics **2** was proved by NMR spectroscopy and elemental analysis (see Experimental section). The protons of the NH-CH groups are presented as two characteristic doublets in ^{1}H NMR spectra. The protons of the CH_2 groups are diastereotopic and give AB-system. The aromatic protons of the compounds **2a**,**c**,**d** are presented as AA'BB' spin system that corresponds to *para*-substituted isomers. ^{1}H NMR spectrum of naphthalene fragment for the compound **2e** points to the formation of 1-naphthyl substituted derivative.

Conclusions

In summary, the method of *C*-amidoalkylation of aromatics with hemiaminal **1** was developed. Possibilities and limitations of the synthetic way to new 2-chloroacetamide derivatives were demonstrated. The synthesis of a series of novel 2-chloro-*N*-(2,2,2-trichloro-1-arylethyl)acetamides, which are of interest as objects of spectroscopic investigation, promising reagents and biologically active compounds or their precursors, was carried out.

Experimental Section

General. NMR spectra were recorded on a Bruker DPX 400 spectrometer (^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz) at 25 °C with HMDS as an internal standard. Chemical shifts are reported in ppm values (δ) and coupling constants (*J*) in Hz. IR spectra were recorded on a Bruker IFS-25 spectrophotometer in KBr. All melting points were measured on a Kofler micro hot stage apparatus. Elemental analyses for C, H and N were obtained using a Thermo Finnigan Flash series1112 EA analyzer. Commercially available CCl_4, aromatics, Lewis and Bronsted acids (Tables 1, 2) were used. 2-Chloro-*N*-(2,2,2-trichloro-1-hydroxyethyl)acetamide **1** was also commercially ordered (Jinan Haohua Industry Co. Ltd., CAS 2755-35-3).

General procedure for C-amidoalkylation of aromatics by hemiaminal (1)

Hemiaminal **1** (2.41 g, 10 mmol), an aromatic (30 mmol), H_2SO_4 (96%, 0.55 mL, ~10 mmol), P_4O_{10} (5 mmol, 1.40 g) in CCl_4 (5 mL) were stirred for the corresponding period (Table 2). Then the reaction mass was mixed with water (50 mL). The organic layer was separated, dried in vacuum and the residue was purified by recrystallization from $CHCl_3$.

2-Chloro-*N*-[2,2,2-trichloro-1-(4-methylphenyl)ethyl]acetamide (2a). IR (ν, KBr, cm^{-1}): 1662 vs (C=O), 2862-2954 m (C-H_{alk}), 3034 m (C-H_{Ar}), 3279 vs br (NH). ^{1}H NMR ($CDCl_3$), δ_H 2.30 (3H, s, CH_3), 4.05, 4.15 (2H, AB, $^2J_{H\text{-}H}$ = 15.3 Hz, CH_2), 5.85 (1H, d, $^3J_{CH\text{-}NH}$ = 9.9 Hz, CH), 7.19, 7.39 (4H, AA′BB′, C_6H_4), 7.65 (1H, $^3J_{CH\text{-}NH}$ = 9.9 Hz, NH). ^{13}C NMR ($CDCl_3$), δ_C 21.15 (CH_3), 45.51 (CH_2Cl), 68.70 (CH), 101.21 (CCl_3), 125.70, 129.18, 135.14, 138.11 (C_6H_4), 165.15 (C=O). Anal. Calcd for $C_{11}H_{11}Cl_4NO$ (315.02): C, 41.94; H, 3.52; Cl, 45.02; N, 4.45%, Found: C, 41.91; H, 3.55; Cl, 45.18; N, 4.51%.

2-Chloro-*N*-[2,2,2-trichloro-1-phenyl)ethyl]acetamide (2b). IR (ν, KBr, cm^{-1}): 1677 vs (C=O), 2880-2953 m (C-H_{alk}), 3067 m (C-H_{Ar}), 3276 vs br (NH). ^{1}H NMR (DMSO-d_6), δ_H 4.21, 4.25 (2H, AB, $^2J_{H\text{-}H}$ = 12.5 Hz, CH_2), 5.88 (1H, d, $^3J_{CH\text{-}NH}$ = 10.0 Hz, CH), 7.40, 7.66 (5H, m, AA′BB′, C_6H_5), 9.47 (1H, $^3J_{CH\text{-}NH}$ = 10.0 Hz, NH). ^{13}C NMR ($CDCl_3$), δ_C 48.18 (CH_2Cl), 70.31 (CH), 101.14 (CCl_3), 126.21, 127.52, 129.31, 135.07 (C_6H_5), 165.73 (C=O). Anal. Calcd for $C_{10}H_9Cl_4NO$ (301.00): C, 39.90; H, 3.01; Cl, 47.11; N, 4.65%, Found: C, 39.85; H, 3.05; Cl, 47.20; N, 4.61%.

2-Chloro-*N*-[2,2,2-trichloro-1-(4-hydroxyphenyl)ethyl]acetamide (2c). IR (ν, KBr, cm^{-1}): 1662 vs (C=O), 3200 vs br (NH), 3260 vs (OH). ^{1}H NMR (acetone-d_6), δ_H 4.20, 4.25 (2H, AB, $^2J_{H\text{-}H}$ = 12.5 Hz, CH_2), 6.38 (1H, d, $^3J_{CH\text{-}NH}$ = 9.5 Hz, CH), 7.05, 7.31 (4H, AA′BB′, C_6H_4), 8.62 д (1H, d, $^3J_{CH\text{-}NH}$ = 9.5 Hz, NH). ^{13}C NMR ($CDCl_3$), δ_C 45.51 (CH_2Cl), 67.82 (CH), 100.59 (CCl_3), 110.11, 118.73, 127.86, 153.14 (C_6H_4), 166.12 (C=O). Anal. Calcd for $C_{10}H_9Cl_4NO_2$ (317.00): C, 37.89; H, 2.86; Cl, 44.74; N, 4.42%, Found: C, 37.92; H, 2.82; Cl, 43.77; N, 4.47%.

2-Chloro-*N*-[2,2,2-trichloro-1-(4-methoxyphenyl)ethyl]acetamide (2d). IR (ν, KBr, cm^{-1}): 1680 vs (C=O), 2869-2948 w (C-H_{alk}), 3065 m (C-H_{Ar}), 3215 vs br (NH). ^{1}H NMR (DMSO-d_6), δ_H 3.77 (3H, s, CH_3), 4.21, 4.26 (2H, AB, $^2J_{H\text{-}H}$ = 12.7 Hz, CH_2), 5.83 (1H, d, $^3J_{CH\text{-}NH}$ = 9.9 Hz, CH), 6.96, 7.59 (4H, AA′BB′, C_6H_4), 9.42 д (1H, d, $^3J_{CH\text{-}NH}$ = 9.9 Hz, NH). ^{13}C NMR ($CDCl_3$), δ_C 43.41 (CH_2Cl), 51.14 (OCH_3), 73.67 (CH), 101.83 (CCl_3), 116.25, 128.18, 131.53, 157.21 (C_6H_4), 167.34 (C=O). Anal. Calcd for $C_{11}H_{11}Cl_4NO_2$ (331.02): C, 39.91; H, 3.35; Cl, 42.84; N, 4.23%, Found: C 39.87; H 3.31; Cl 43.69; N 4.17%.

2-Chloro-*N*-[2,2,2-trichloro-1-(naphth-1-yl)ethyl]acetamide (2e). IR (ν, KBr, cm^{-1}): 1680 vs (C=O), 2870, 2947 w (C-H_{alk}), 3002-3065 w (C-$H_{аром.}$), 3276 vs br (NH). ^{1}H NMR (DMSO-d_6), δ_H 4.22, 4.27 (2H, AB, $^2J_{H\text{-}H}$ = 12.1 Hz, CH_2), 6.93 (1H, d, $^3J_{CH\text{-}NH}$ = 9.5 Hz, CH), 7.57, 7.63, 7.91-8.08, 8.29 (7H, m, $C_{10}H_7$), 9.67 (1H, d, $^3J_{CH\text{-}NH}$ = 9.5 Hz, NH). ^{13}C NMR (DMSO-d_6), δ_C 45.53 (CH_2Cl), 76.21 (CH), 102.14 (CCl_3), 122.11, 123.31, 125.48, 126.75, 127.41, 129.41, 129.93, 131.80, 132.56, 140.20 ($C_{10}H_7$), 168.72 (C=O). Anal. Calcd for $C_{14}H_{11}Cl_4NO$ (351.05): C, 47.90; H, 3.16; Cl, 40.40; N, 3.99%, Found: C, 47.97; H, 3.18; Cl, 40.31; N, 3.93%.

2-Chloro-*N*-[2,2,2-trichloro-1-(5-chlorothien-2-yl)ethyl]acetamide (2f). IR (ν, KBr, cm^{-1}): 1678 vs (C=O), 3065-3101 w (C-H_{Ar}), 3276 vs br (NH). ^{1}H NMR (DMSO-d_6), δ_H 4.17, 4.23 (2H, AB, $^2J_{H\text{-}H}$ = 13.0 Hz, CH_2), 6.05 (1H, d, $^3J_{CH\text{-}NH}$ = 9.5 Hz, CH), 7.03, 7.26 (2H, AB, $^3J_{H\text{-}H}$ = 3.8 Hz, 5-chlorothien-2-yl), 9.53 (1H, d, $^3J_{CH\text{-}NH}$ = 9.5 Hz, NH). ^{13}C NMR (DMSO-d_6), δ_C 43.67 (CH_2Cl), 68.15 (CH), 100.35 (CCl_3), 125.42, 133.87, 143.63, 146.80 (5-chlorothien-2-yl), 166.30 (C=O). Anal. Calcd for $C_8H_6Cl_5NOS$ (341.47): C, 28.14; H, 1.77; Cl, 51.91; N, 4.10; S, 9.39%, Found: C 28.17; H 1.73; Cl 51.98; N 4.07; S 9.28%.

2,2′-(2,2,2-trichloroethane-1,1-diyl)bis(5-chlorothiophene) (3). The compound **3** was detected by NMR spectroscopy in the reaction mixture when the synthesis of **2f** was carried out for 10 h. ^{1}H NMR (DMSO-d_6), δ_H 6.21 (1H, s, CH), 6.99, 7.18 [4H, AB, bis(5-chlorothien-2-yl)]. ^{13}C NMR (DMSO-d_6), δ_C 62.22 (CH), 100.18 (CCl_3), 127.22, 135.40, 144.80, 147.23 (5-chlorothien-2-yl). The spectral data obtained are in accordance with literature data.[30]

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