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Halogenation of terminal acetylenes by perhalogenoalkanes under phase transfer catalysis conditions

Edgars Abele, Mendel Fleisher, Kira Rubina,
Ramona Abele, Edmunds Lukevics*

Latvian Institute of Organic Synthesis, 21 Aizkraukles Str., LV-1006, Riga, Latvia

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Abstract

Halogenation of terminal acetylenes by perhalogenoalkanes such as CCl_4, CBr_4 and CI_4 under phase transfer catalysis conditions was studied. The influence of base and halogenating agent amounts on process of phenylacetylene bromination and iodination was discussed. The quantum chemical calculations of bromination of 2-pyridylacetylene using the semiempirical AM1 method were carried out. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Phase transfer catalysis; Terminal acetylenes; Semiempirical AM1 method

1. Introduction

Halogenated terminal acetylenes are intensively studied as intermediates in the synthesis of biologically active compounds. For example, chlorinated terminal acetylenes usually are obtained from terminal acetylenes by chlorination with *n*-BuLi/NCS [1], *n*-BuLi/Cl_2 [2], HOCl [3,4] and CCl_4/50% aq. NaOH/Et_3BnNCl [5]. Brominated acetylenes are prepared from terminal acetylenes and CBr_4/PPh_3 [6], NaBr/NaOCl/Bu_4NHSO_4 [7], *n*-BuLi/NBS [8], *n*-BuLi/Br_2 [2], NaOH/Br_2 [9], DBU/CCl_3Br [10], CuBr/$(Me_3SiO)_2$ [11], NBS/$AgNO_3$ [12] or hypobromites [4]. Iodination of terminal acetylenes successfully can be carried out in the presence of I_2/KI/KOH [13], I_2/cat. CuI/K_2CO_3 or Na_2CO_3/Bu_4NCl [14], I_2/*n*-BuLi [15], EtMgBr/I_2 [16], CuI or $ZnI_2/(Me_3SiO)_2$ [11], NaOMe/$I(Py)_2BF_4$ [17], Li/NH_3/*n*-C_3H_7I [18] and $[I(collidine)_2]PF_6$ [19]. Recently we have described preliminary results of some terminal acetylenes bromination by carbon tetrabromide under phase transfer catalysis (PTC) conditions [20].

2. Experimental

2.1. Materials and methods

GC analysis was performed on a Chrom-5 instrument equipped with a flame-ionization detector using a glass column packed 5% OV-101/Chromosorb W-HP (80–100 mesh), 1.2 m × 3 mm. *O*-propargyloximes were prepared from corresponding carbonyl com-

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[*] Corresponding author. Tel.: +371-7551822;
fax: +371-7821038.
E-mail addresses: misha@osi.lv (M. Fleisher), kira@osi.lv (E. Lukevics).

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Table 1
PTC chlorination of terminal acetylenes

Alkyne	R	Reaction time (h)	Product	Isolated yield (%)	Reference
1b	2-Pyridyl	3	**2b**	40	[23]
1c	3-Pyridyl	3	**2c**	49	[23]
1d	2-Methyl-5-pyridyl	2	**2d**	52	[23]
1f	(2-Furyl)C(Me)$=$NOCH$_2$	10	**2f**	49	[24]
1h	(2-Thienyl)C(Me)$=$NOCH$_2$	20	**2h**	46	[24]

pounds according to literature data [21]. Pyridylacetylenes were prepared from corresponding vinylpyridines [22].

2.2. Typical procedure for chlorination of terminal acetylenes

Finely powdered KOH (0.168 g, 3 mmol) was added to a solution of acetylene (**1**) (1 mmol) and 18-crown-6 (0.013 g, 0.05 mmol) in CCl_4 (1 ml). The reaction mixture was refluxed for 2–20 h. The solid substance was filtered off and the filtrate evaporated under reduced pressure. The residue was purified by column chromatography (Table 1).

2.3. Typical procedure for bromination of terminal acetylenes

Finely powdered KOH (0.336 g, 6 mmol) was added to a solution of acetylene (**1**) (2 mmol), CBr_4 (0.498 g, 1.5 mmol) and 18-crown-6 (0.026 g, 0.1 mmol) in benzene (2 ml). The reaction mixture was stirred for 2–12 h at room temperature. The solid substance was filtered off and the filtrate evaporated under reduced pressure. The residue was purified by column chromatography (Tables 2 and 3).

2.4. Typical procedure for iodination of phenylacetylene

Finely powdered KOH (2 or 3 mmol, see Table 4) was added to a solution of phenylacetylene (**1a**) (1 mmol), CI_4 (0.75 or 1 mmol) and 18-crown-6 (0.013 g, 0.05 mmol) in benzene (1.5 ml). The reaction mixture was stirred for 6–10 h at room temperature with GLC and GLC-MS control (Table 4).

2.5. Calculations

All calculations were carried out with the semiempirical AM1 [25] method as implemented in MOPAC 6 [26]. The equilibrium geometries were obtained with complete optimization at PRECISE level. The all optimum structures present the minimum points on the

Table 2
PTC bromination of phenylacetylene (**1a**) under PTC conditions[a]

Base (equiv.)	Catalyst	CBr_4 (equiv.)	Reaction time (h)	Yield of (**3a**) (%) (GLC data)
KOH (3)	18-crown-6	0.5	13	58
KOH (3)	18-crown-6	0.75	11	79
KOH (3)	18-crown-6	1.0	11	67
KOH (2)	18-crown-6	1.5	8	42
KOH (3)	18-crown-6	1.5	8	36
K_2CO_3 (3)	18-crown-6	1.0	9	0
KF (3)	18-crown-6	1.0	9	22
50% KOH (4 ml)	$BnEt_3NCl$	1.5	8	41
KOH (3)	18-crown-6	1.0[b]	11	6

[a] Reaction conditions: phenylacetylene (0.11 ml, 1 mmol), catalyst (0.05 mmol), base and brominating agent see Table in benzene (1 ml), 20°C.

[b] $CHBr_3$ as brominating agent.

Table 3
PTC bromination of terminal acetylenes

Alkyne	R	Reaction time (h)	Product	Isolated yield (%)	Reference
1b	2-Pyridyl	4	**3b**	66	[20]
1c	3-Pyridyl	7	**3c**	60	[20]
1d	2-Methyl-5-pyridyl	12	**3d**	42	[20]
1e	(2-Furyl)CH=NOCH$_2$	10	**3e**	52	[24]
1f	(2-Furyl)C(Me)=NOCH$_2$	6	**3f**	72	[24]
1g	(2-Thienyl)CH=NOCH$_2$	7	**3g**	65	[24]
1h	(2-Thienyl)C(Me)=NOCH$_2$	2	**3h**	84	[20]
1I	(2-Pyridyl)CH=NOCH$_2$	4	**3I**	59	[20]
1j	(3-Pyridyl)CH=NOCH$_2$	4	**3j**	64	[20]
1k	(4-Pyridyl)CH=NOCH$_2$	4	**3k**	42	[20]
1m	PhCH$_2$OCH$_2$	2	**3m**	37	[20]
1n	CH$_3$(CH$_2$)$_3$	10	**3n**	62	

Table 4
Iodination of phenylacetylene (**1a**) by carbon tetraiodide under PTC conditions[a]

KOH (equiv.)	CI$_4$ (equiv.)	Reaction time (h)	Yield of (**4a**) (%) (GLC data)
3	1	6	84
2	1	10	90
3	0.75	10	87
2	0.75	10	94
2	1[b]	8	10

[a] For reaction conditions see Section 2.
[b] CHI$_3$ as iodinating agent.

potential energy surface as the frequency analysis has shown. A keyword PARASOK was applied in the calculations of the lithium cation containing structures [27]. To obtain the data on the change in geometry[1] during the optimization process, calculations were performed using a keyword FLEPO.

Post processing animation was carried out with Xmol [28] and Jmol [29] programs.

3. Results and discussion

Reactions of terminal acetylenes halogenation were carried out using perhalogenoalkanes as sources of positive halogen. Positive halogen ions are generated exclusively by interaction of carbon tetrahalide with carbanion (acetylenide anion) [30,31]. The latter is formed from corresponding acetylene in PTC system solid KOH/18-crown-6.

$$\underset{\mathbf{1}}{\mathrm{R{-}C{\equiv}CH}}\xrightarrow[\text{solvent}]{\mathrm{CX_4/KOH/18\text{-}crown\text{-}6}}\underset{\mathbf{2\text{–}4}}{\mathrm{R{-}C{\equiv}CX}}$$

The solid/liquid PTC system solid KOH/18-crown-6/CCl$_4$was found to be the best for the chlorination of different types of terminal acetylenes (see Section 2 and Table 1). In the presence of this catalytic system chlorinated acetylenes **2b–d**, **f** and **h** were obtained in 40–52% yields.

The processes of bromination and iodination of phenylacetylene by CBr$_4$ and CI$_4$ were investigated in details with aim to found the best catalyst, base and halogenating agent ratio.

The PTC system CBr$_4$ (0.75 equiv. to phenylacetylene (**1a**))/solid KOH/18-crown-6 in benzene was found to be the most active in synthesis of phenylbromoacetylene (**3a**) (Table 2). Increase in the amount of CBr$_4$ to 1 equiv. or more, diminishes the yield of (**3a)** due to brominated product side reactions (for exam-

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[1] Multi-structure XYZ format files, containing data of the change of system geometry and energy during the reaction of 2-pyridylacetylene bromination. This material is available from the authors on request (Dr. M. Fleisher).

ple, formation of polybrominated products). Presence of bromoform as second product was detected in all reaction mixtures. The formation of addition products of dibromocarbene generated from bromoform and carbon tetrabromide to C≡C triple bonds was not observed.

The systems, solid CBr_4/KF/18-crown-6 and CBr_4/50% aq. KOH/$BnEt_3NCl$, were less active in bromination of (**1a**). Surprisingly, bromination of (**1a**) also proceeds in the presence of PTC system $CHBr_3$ (1 equiv.)/solid KOH/18-crown-6. Brominated product PhC≡CBr was obtained in 6% yield. However, it was known that bromoform can not be a source of Br^+ ion. Thus, carbon tetrabromide could be formed in situ from bromoform in the presence of the base. Such type “halogen dance reactions” in dihalo-, trihalo- and tetrahalomethanes in the presence of base are described in some articles [32–34].

The PTC system CBr_4 (0.75 equiv.)/solid KOH/18-crown-6/benzene as the most active was used in the bromination of terminal acetylenes of different types (see Section 2 and Table 3).

The influence of KOH and CI_4 amount was studied in the phenylacetylene iodination reaction. The best yield of phenyliodoacetylene (**4a**) (94%) was obtained in the PTC system solid CI_4 (0.75 equiv.)/KOH (2 equiv.)/18-crown-6/benzene at room temperature (GLC data, see Table 4). Increase in the amount of KOH or carbon tetraiodide diminishes the yield of desired product PhC≡CI because of side reactions (for example, formation of 1-phenyl-1,2-diiodoethene, mass-spectroscopy data). Iodination of (**1a**) also proceeds in the presence of PTC system CHI_3 (1 equiv.)/solid KOH/18-crown-6. Iodinated product in this case was obtained only in 10% yield. Carbon tetraiodide formed in situ from iodoform in the presence of the base similarly as in the case of the bromination process.

3.1. Mechanism of bromination

The quantum chemical study on example of 2-pyridylacetylene bromination was carried out.

It is known that 18-crown-6 acts as “organic masking” agent for alkali metal. It provides “onium ion”-like entity that can be extracted or solubilized with the accompanying anion into organic solvent [35]. Thereby OH^--group is transferred into benzene.

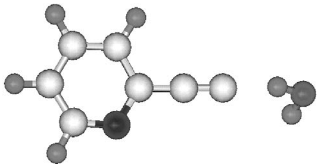

Fig. 1.

We suppose that the first reaction step is the interaction of the OH^--group with the terminal proton of 2-pyridylacetylene. As the calculations have shown reaction proceeded with $PyC≡C^-$ ion and H_2O molecule formation without any activation barrier (Fig. 1). The reaction heat is −42.449 kcal/mol.

The water molecule take-off needs 12.105 kcal/mol. The strongly polarized water molecule reacted further with potassium cation forming (K^+H_2O)-complex.

The second step of reaction is the interaction of pyridyl acetylenide anion with CBr_4. The equilibrium structure of the complex containing Br-bridge atom is formed (Fig. 2).

The order of the $PyC≡C^-\cdots$Br-bond is 0.699 and $Br\cdots CBr_3$-bond is 0.340. The heat of the complex formation is equal −70.765 kcal/mol.

The last reaction step includes the hydrated counterion (K^+H_2O) attack on the most electronegative carbon atom in CBr_4 part of the $(2\text{-Py-C}≡\text{C}\cdots\text{Br}\cdots\text{CBr}_3)^-$-complex. The charge of this atom is equal −0.602*e*.

Fig. 3 shows the most essential moments of the latter reaction step, i.e. bromoform breaking from an intermediate set carbanion-CBr_4. In the initial position (Fig. 3a) a stable intermediate set carbanion-CBr_4 is affected by solvated ion (K^+H_2O). In the process of the set and K^+H_2O approach, the proton breaks off from the latter (Fig. 3b). Then the C–Br bond in CBr_4 breaks and synchronously bromoform is formed. The results of the catalytic cycle completion are given in Fig. 3c. The calculated reaction heat is −220.411 kcal/mol.

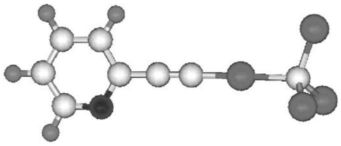

Fig. 2.

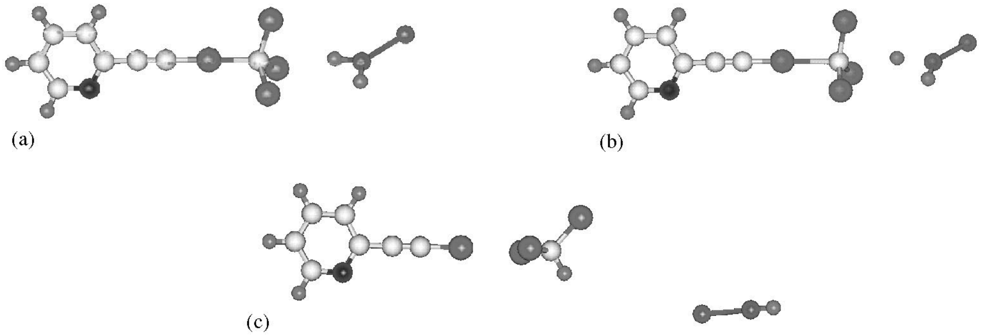

Fig. 3.

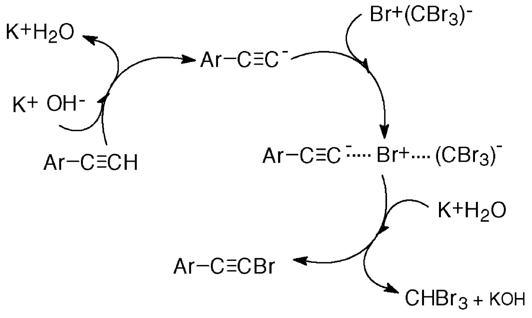

Fig. 4.

4. Conclusions

The experiments showed that chlorination, bromination and iodination of different types of terminal acetylenes by perhaloalkanes could be easily carried out under phase transfer catalysis conditions. Activity of halogenating agent diminishes in order $CI_4 > CBr_4 \gg CCl_4$. The quantum chemical calculations allow to propose the following mechanism of terminal acetylenes bromination process (Fig. 4).

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