
Bis(4-dialkylaminopyridinium-1-yl)alkylene halides as phase-transfer catalysts in the reactions of dichlorocarbene

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α,ω -Bis(4-dialkylaminopyridinium-1-yl)alkylene halides (obtained by quaternization of 4-dimethylamino- and 4-morpholinopyridines with α,ω -alkylene dihalides) are effective phase-transfer catalysts in typical two-phase reactions of dichlorocarbene – dehydration of benzamide and dichlorocyclopropanation of styrene. Catalytic activity of the above bis-quaternary salts is similar to that of conventional quaternary ammonium catalysts, but they can be used in lower concentrations due to the presence of two cationic centres per one molecule.

Key words: Phase-transfer catalysis, carbenes, quaternary pyridinium salts, α,ω -bis(4-dialkylaminopyridinium-1-yl)alkylene halides; 4-dimethylaminopyridine

INTRODUCTION

Phase-transfer catalytic (PTC) method of the generation of dihalocarbenes has been in widest use for more than 30 years [1, 2]. In the majority of applications, quaternary ammonium salts were the catalysts of choice due to their convenient and cheap preparation [3]. The leading scientists of the field, including M. Makosza [4], held small, hydrophilic catalysts such as benzyltriethylammonium chloride (TEBA) and tetraethylammonium bromide (TEAB) to be optimal for the reactions of that type [3–5]. Therefore the choice from other types of quaternary ammonium catalysts was relatively limited, although different authors pointed out that more lipophilic quaternary salts with bulky alkyl substituents should be more stable in the presence of concentrated aqueous alkaline solutions [6, 7]. The search for new stable, active as well as selective PT catalysts resulted in numerous articles and patents [8–13]. From these novel catalysts, quaternary pyridinium salts are particularly attractive because of enhanced thermal stability and easy recovering from the reaction mixture. These advantages are particularly valuable in nucleophilic aromatic substitution where high temperatures are normally employed [12]. Meanwhile, bis-quaternary aminopyridinium salts having the ability to carry bivalent anions into the organic phase are highly suitable catalysts for the alkylation of phenoxides such as bisphenol A [13].

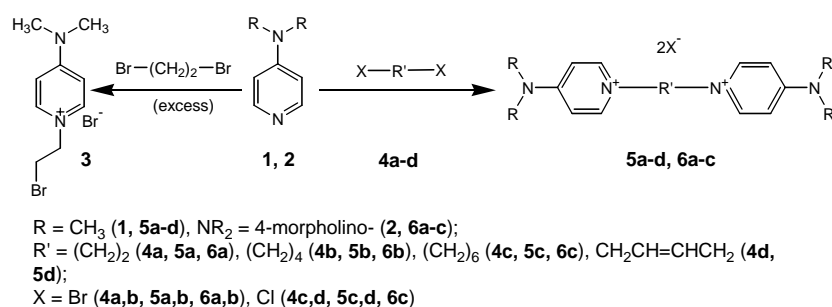
Recently we have studied pyridylsulfobetaines and 1-alkyl-4-dialkylaminopyridinium halides in various PTC reactions of dichlorocarbene where some of them showed outstanding catalytic properties [14, 15]. As a continuation of our study on PTC, now we explored bis-quaternary pyridinium salts derived from 4-dimethylamino- and 4-morpholinopyridine.

RESULTS AND DISCUSSION

In the present work we aimed to synthesize a series of bis-quaternary halides by quaternization of 4-dimethylamino- (**1**) and 4-morpholinopyridine (**2**) with dihaloalkanes. Depending on the ratio of reactants, alkylation of aminopyridines with bifunctional alkyl halides can give either mono- (excess of alkylating agent) or bis- (excess of nucleophile) quaternary pyridinium salts. Alkylation in the absence of base normally occurs on the ring nitrogen as the more nucleophilic [16]. However, 2-dimethylaminopyridine is anomalous in undergoing further methylation on the exocyclic nitrogen [17]. In order to check the alkylation route, we performed the quaternization of 4-dimethylaminopyridine with ninefold excess of 1,2-dibromoethane. The only isolable product was 1-(2-bromoethyl)-4-dimethylaminopyridinium bromide (**3**) confirming that alkylation occurs exclusively at 1-position of the pyridine ring.

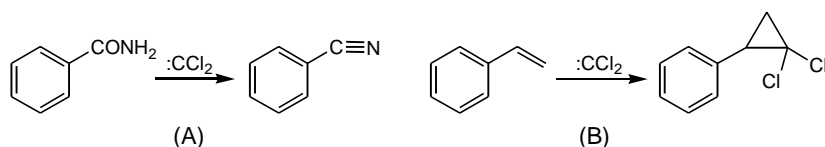
The treatment of 2 equivalents of 4-dialkylaminopyridines **1**, **2** with 1 equivalent of the correspon-

ding alkylene dihalide **4 a-d** (1,2-dibromoethane, 1,4-dibromobutane, 1,6-dichlorohexane, 1,4-dichloro-2-butene) in DMFA afforded α,ω -bis(4-dialkylaminopyridinium)alkylene dihalides **5 a-d**, **6 a-c** (Scheme 1).



After recrystallization from ethanol they appeared as colourless crystalline solids. The structure of the synthesized compounds was confirmed by spectral data. In ¹H NMR spectra the signals of α -methylene protons (CH₂-N⁺) appear at 3.95–4.63 ppm, depending on methylene chain length between two pyridine rings. The signal of CH₂-Br at 3.90 ppm is present only in the spectrum of mono-quaternary salt **3** and is totally absent in the spectra of bis-quaternary salts **5 a-d**, **6 a-c**. In the IR spectra, a characteristic absorption band of C=N⁺ stretching vibrations is present at 1650–1630 cm⁻¹.

Bis-quaternary salts **5 a-d**, **6 a-c** were tested as PT catalysts in standard two-phase reactions of dichlorocarbene: dehydration of benzamide (reaction A) and dichlorocyclopropanation of styrene (reaction B) (Scheme 2).



EXPERIMENTAL

Melting points (open capillaries) are uncorrected. IR spectra (KBr) were recorded on a FT-IR spectrometer BOMEM (Hartmann & Braun, Canada). ¹H NMR spectra were recorded on a Tesla BS-567A NMR spectrometer at 80 MHz with TMS as internal standard. GC analysis was performed on a Hewlett Packard instrument HP 5890 equipped with flame-ionization detector and silica capillary column, CP-Sil

Catalyst	Reaction A ^a		Reaction B ^a	
	Catalyst concentration, mol. %	Product yield, % ^b	Catalyst concentration, mol. %	Product yield, % ^b
5a	2.5	71	2	99
5b	2.5	76	2	89
5c	2.5	70	2	96
5d	2.5	41	–	–
6a	2.5	66	2	58
6b	2.5	65	2	53
6c	2.5	62	2	57
–	0	7.5	0	<1
TEBA	5	61	1	71
TBAB	–	–	2	94

^a For reaction conditions see Experimental; ^b GC control.

For comparison, two commercial PT catalysts, TEBA and tetrabutylammonium bromide (TBAB), were also tested. Results of the kinetic study are summarized in Table 1. As one can see, bis-quaternary salts **5 a-d**, **6 a-c** show catalytic properties generally comparable to those of conventional PT catalysts. The only exception is **5d**; in this case, concurrent reaction of the double C=C bond of the catalyst with dichlorocarbene obviously takes place, thus diminishing its catalytic activity.

In our previous study of 1-alkyl-4-dialkylaminopyridinium salts [15], we noticed a pronounced influence of 1-alkyl chain length on the catalytic properties. In a series of bis-quaternary salts **5 a-d**, **6 a-c**, methylene chain length plays no major role. Meanwhile, the influence of 4-dialkylamino substituent is more evident. The yield of 1,1-dichloro-2-phenylcyclopropane (reaction B) in the presence of 2 mol. % of catalysts **5 a-c** derived from 4-dimethylaminopyridine is nearly quantitative, while in the presence of **6 a-c** (from 4-morpholinopyridine) it is only moderate. A similar phenomenon was also observed in the previous study [15].

It is of major importance that high yields of benzonitrile (reaction A) are achieved with a twice-lower catalyst concentration due to two quaternary nitrogen atoms per one molecule, while conventional catalysts are usually employed for dehydration of amides at 5 mol. % concentration.

8CB (50 m × 0.32 mm i.d., film thickness 0.25 μm). The same analysis conditions as in GC were used in GC-MS. Mass spectra in electron mode were generated at 70 eV. Qualitative analysis was based on the comparison with mass spectral libraries and retention time. Elemental analyses (C, H, N) are in satisfactory agreement with the calculated values.

Commercial 4-dimethylaminopyridine (MERCK) was used. 4-Morpholinopyridine (**2**) was prepared from 4-nitropyridine-1-oxide as described in [15].

1-(2-Bromoethyl)-4-dimethylaminopyridinium bromide (**3**)

A solution of 12.22 g (0.1 mol) of 4-dimethylaminopyridine **1** in 100 ml of acetone was added dropwise upon stirring to 77.6 ml (0.9 mol) of 1,2-dibromoethane **4a**. The mixture was stirred under reflux for 5 h. The solid was filtered, washed with acetone, dried in vacuo (P₂O₅) and recrystallized from 2-propanol.

Yield of (**3**) 96%. M. p. 190–192 °C. IR (KBr): $\nu = 2925, 1635, 1560 \text{ cm}^{-1}$. ¹H NMR (D₂O, δ , ppm): 8.11 (2H, d, Py-2H), 6.96 (2H, d, Py-3H), 4.61 (2H, t, N⁺-CH₂), 3.90 (2H, t, CH₂-Br), 3.26 (6H, s, N-CH₃). Found, %: C 34.57; H 4.51; N 9.20. C₉H₁₄Br₂N₂. Calc., %: C 34.86; H 4.55; N 9.04.

α,ω -Bis(4-dimethylaminopyridinium-1-yl)alkylene dihalides (**5 a–d**)

To a solution of 4-dimethylaminopyridine **1** (0.02 mol) in 10 ml of dimethylformamide, 0.01 mol of the corresponding dihaloalkane **4 a–d** was added dropwise. The reaction mixture was heated at 90–100 °C for 3–5 h (see below). The solid product was filtered, washed with acetone, dried in vacuo (P₂O₅) and recrystallized from ethanol.

1,2-Bis(4-dimethylaminopyridinium-1-yl)ethane dibromide (**5a**)

From **1** and **4a** (3 h). Yield 61% (from ethanol). M. p. 310–312 °C (decomp.). IR (KBr): $\nu = 2925, 1635, 1560 \text{ cm}^{-1}$. ¹H NMR (CD₃CN + D₂O, δ , ppm): 7.98 (4H, d, Py-2H), 6.82 (4H, d, Py-3H), 4.57 (4H, m, N⁺-CH₂), 3.19 (12H, s, N-CH₃). Found, %: C 44.27; H 5.51; N 13.00. C₁₆H₂₄Br₂N₄. Calc., %: C 44.46; H 5.60; N 12.96.

1,4-Bis(4-dimethylaminopyridinium-1-yl)butane dibromide (**5b**)

From **1** and **4b** (3 h). Yield 87% (from ethanol). M. p. 263–264 °C. IR (KBr): $\nu = 1640, 1555 \text{ cm}^{-1}$. ¹H NMR (CD₃CN + D₂O, δ , ppm): 7.86 (4H, d, Py-2H), 6.72 (4H, d, Py-3H), 4.02 (4H, m, N⁺-CH₂), 3.06

(12H, s, N-CH₃), 1.73 (4H, m, N⁺-CH₂-CH₂). Found, %: C 47.05; H 6.18; N 12.04. C₁₈H₂₈Br₂N₄. Calc., %: C 46.97; H 6.13; N 12.17.

1,6-Bis(4-dimethylaminopyridinium-1-yl)hexane dichloride (**5c**)

From **1** and **4c** (5 h). Yield 76% (from 75% aq. ethanol). M. p. 292–293 °C (with decomp.). IR (KBr): $\nu = 2970, 2880, 1640, 1565 \text{ cm}^{-1}$. ¹H NMR (CD₃CN + D₂O, δ , ppm): 7.80 (4H, d, Py-2H), 6.69 (4H, d, Py-3H), 3.95 (4H, m, N⁺-CH₂), 3.04 (12H, s, N-CH₃), 1.67 (4H, m, N⁺-CH₂-CH₂), 1.20 (4H, m, N⁺-CH₂-CH₂-CH₂). Found, %: C 60.02; H 8.22; N 13.90. C₂₀H₃₂Cl₂N₄. Calc., %: C 60.14; H 8.08; N 14.03.

1,4-Bis(4-dimethylaminopyridinium-1-yl)but-2-ene dichloride (**5d**)

From **1** and **4d** (3 h). Yield 98% (from ethanol). M. p. 295–297 °C (decomp.). IR (KBr): $\nu = 3010, 2905, 1640, 1563 \text{ cm}^{-1}$. ¹H NMR (CD₃CN + D₂O, δ , ppm): 7.87 (4H, d, Py-2H), 6.77 (4H, d, Py-3H), 5.82 (2H, m, CH=CH), 4.63 (4H, m, N⁺-CH₂), 3.07 (12H, s, N-CH₃). Found, %: C 58.44; H 7.15; N 15.03. C₁₈H₂₆Cl₂N₄. Calc., %: C 58.53; H 7.10; N 15.17.

α,ω -Bis(4-morpholinopyridinium-1-yl)alkylene dihalides (**6 a–c**)

Prepared analogously to **5 a–d** using 0.01 mol of 4-morpholinopyridine **2** and 0.005 mol of dihaloalkane **4 a–c**.

1,2-Bis(4-morpholinopyridinium-1-yl)ethane dibromide (**6a**)

From **2** and **4a** (4 h). Yield 70% (ethanol). M. p. 307–309 °C (with decomp.). IR (KBr): $\nu = 2970, 1640, 1540 \text{ cm}^{-1}$. ¹H NMR (D₂O, δ , ppm): 8.13 (4H, d, Py-2H), 7.12 (4H, d, Py-3H), 4.61 (4H, m, N⁺-CH₂), 3.84 (8H, m, O-CH₂), 3.74 (8H, m, N-CH₂). Found, %: C 46.21; H 5.28; N 10.63. C₂₀H₂₈Br₂N₄O₂. Calc., %: C 46.52; H 5.47; N 10.85.

1,4-Bis(4-morpholinopyridinium-1-yl)butane dibromide (**6b**)

From **2** and **4b** (4 h). Yield 91% (ethanol). M. p. 267–268 °C. IR (KBr): $\nu = 3043, 2962, 2861, 1644, 1542 \text{ cm}^{-1}$. ¹H NMR (D₂O, δ , ppm): 8.09 (4H, d, Py-2H), 7.09 (4H, d, Py-3H), 4.23 (4H, m, N⁺-CH₂), 3.85 (8H, m, O-CH₂), 3.76 (8H, m, N-CH₂), 1.92 (4H, m, N⁺-CH₂-CH₂). Found, %: C 48.70; H 6.04; N 10.19. C₂₂H₃₂Br₂N₄O₂. Calc., %: C 48.54; H 5.93; N 10.29.

1,6-Bis(4-morpholinopyridinium-1-yl)hexane dichloride (6c)

From **2** and **4c** (4 h). Yield 48% (2-propanol : ethanol 2:1). M. p. 296–298 °C (with decomp.). IR (KBr): $\nu = 3056, 2920, 2863, 1648, 1545 \text{ cm}^{-1}$. ^1H NMR (D_2O , δ , ppm): 8.10 (4H, d, Py-2H), 7.09 (4H, d, Py-3H), 4.18 (4H, t, $\text{N}^+\text{-CH}_2$), 3.87 (8H, t, O-CH_2), 3.78 (8H, t, N-CH_2), 1.88 (4H, m, $\text{N}^+\text{-CH}_2\text{-CH}_2$), 1.37 (4H, m, $\text{N}^+\text{-CH}_2\text{-CH}_2\text{-CH}_2$). Found, %: C 59.51; H 7.71; N 11.39. $\text{C}_{24}\text{H}_{36}\text{Cl}_2\text{N}_4\text{O}_2$. Calc., %: C 59.62; H 7.51; N 11.59.

General procedures for PTC reactions

Dehydration of benzamide. A mixture of benzamide (0.05 mol), CHCl_3 (35 ml), catalyst (2.5–5 mol. %) and 40% aq. NaOH (12 ml) was stirred at 50 °C for 4 h. Samples (0.2 ml each) were withdrawn periodically (usually every 30 min) from the organic layer, diluted with CHCl_3 (3 ml) and subjected to GC and GC-MS analysis. Conversions were derived from the ratio of benzonitrile to nonane as internal standard.

Dichlorocyclopropanation of styrene. A mixture of styrene (0.05 mol), CHCl_3 (35 ml), catalyst (1–2 mol. %) and 50% aq. NaOH (8 ml) was stirred at 40 °C for 3 h with GC and GC-MS monitoring as described in the previous section. Conversions were derived from the ratio of 1,1-dichloro-2-phenylcyclopropane to nonane as internal standard.

CONCLUSIONS

1. Quaternization of 2 equivalents of 4-dimethylamino- and 4-morpholinopyridine with 1 equivalent of alkylene dihalide gives α,ω -bis(4-dialkylaminopyridinium)alkylene dihalides with high or moderate yields.

2. The synthesized bis-quaternary salts exhibit catalytic activity in typical PTC reactions of dichlorocarbene, similar to that of TEBA and TBAB. Due to the presence of two quaternary N atoms per one molecule these catalysts can be used at lower concentrations.

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BIS(4-DIALKILAMINOPIRIDINIO-1)ALKILENŲ HALOGENIDAI – TARPFAZINIAI KATALIZATORIAI DICHLORKARBENO REAKCIJOJE

S a n t r a u k a

α,ω -Bis(4-dialkilaminopiridinio-1)alkilenų halogenidai (sintetinti kvaternizuojant 4-dimetilamino- ir 4-morfolinopiridinus alkilenų dihalogenidais) efektyviai katalizuoja būdingas dvifazes dichlorkarbeno reakcijas – benzamido dehidrataciją ir stireno dichlorciklopropilimą. Šių bis-ketvirtinių druskų katalitinis aktyvumas yra panašus į įprastų ketvirtinių amonio katalizatorių aktyvumą, tačiau dėl dviejų katijoninių centrų, esančių vienoje molekulėje, juos galima naudoti mažesnėmis koncentracijomis.

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БИС(4-ДИАЛКИЛАМИНОПИРИДИНИЙ-1)АЛКИЛЕНДИГАЛОГЕНИДЫ – МЕЖФАЗНЫЕ КАТАЛИЗАТОРЫ В РЕАКЦИЯХ С УЧАСТИЕМ ДИХЛОРКАРБЕНА

Р е з ю м е

α,ω -Бис(4-диалкиламинопиридиний-1)алкилендигалогениды (полученные кватернизацией 4-диметиламино- и 4-морфолинопиридинов алкилендигалогенидами) эффективно катализируют двухфазные реакции с участием дихлоркарбена – дегидратацию бензамида и дихлорциклопропанирование стирола. Каталитическая активность данных бис-четвертичных солей сравнима с активностью обычных четвертичных аммониевых катализаторов, но благодаря наличию двух катионных центров в одной молекуле их можно использовать в меньших концентрациях.