Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# Reactions of π-Deficient Aromatic Heterocycles with Ammonium Polyhalides I. Halogenation of Acridone and Acridine Derivatives Using Benzyltriethylammonium (BTEA) Polyhalides

Mircea Vlassa [a], Ioan A. Silberg [a], Radu Custelceanu [a] & Monica Culea [b]

[a] Babe[stilde]-Bolyai University, Faculty of Chemistry, 11 Arany Janos st., 3400, Cluj-Napoca, Romania

[b] Institute of Isotopic and Molecular Technology, 3400, Cluj-Napoca, Romania

Published online: 23 Sep 2006.

To cite this article: Mircea Vlassa , Ioan A. Silberg , Radu Custelceanu & Monica Culea (1995) Reactions of π-Deficient Aromatic Heterocycles with Ammonium Polyhalides I. Halogenation of Acridone and Acridine Derivatives Using Benzyltriethylammonium (BTEA) Polyhalides, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:21, 3493-3501, DOI: 10.1080/00397919508013873

To link to this article: http://dx.doi.org/10.1080/00397919508013873

SYNTHETIC COMMUNICATIONS, 25(21), 3493-3501 (1995)

# REACTIONS OF π-DEFICIENT AROMATIC HETEROCYCLES WITH AMMONIUM POLYHALIDES I.HALOGENATION OF ACRIDONE AND ACRIDINE DERIVATIVES USING BENZYLTRIETHYLAMMONIUM ( BTEA ) POLYHALIDES

Mircea Vlassa*, Ioan A. Silberg, Radu Custelceanu and Monica Culea**

* Babeş-Bolyai University, Faculty of Chemistry, 11 Arany Janos st., 3400 Cluj-Napoca, Romania.
** Institute of Isotopic and Molecular Technology, 3400 Cluj-Napoca, Romania.

**ABSTRACT.** The reactions of acridine and acridone with benzyltriethylammonium polyhalides in various solvents, under mild conditions, gave mono- and dihalogenated acridine and acridone derivatives and acridine complexes in good yields.

Since acridine and acridone derivatives are sensitive toward electrophilic substitution reactions, their direct halogenation yields mixture of mono-, di- and polysubstituted derivatives[1-6]. Ring closure of the corresponding diphenylamino-

* To whom correspondence should be addressed.

-2-carboxylic acids substituted with halogens or with nitro groups, which are transformed in their turn, after cyclization, by Sandmayer reaction, to the respective halogenated derivatives, is another route to obtain such compounds[7-18]

The above mentioned methods are tedious and generally give low yields. For improving the procedure for preparation of halogenated compounds we tried to use benzyltriethylammonium polyhalides. Halogenation with quaternary ammonium polyhalides was widely applied since 1987 in the class of aliphatic and aromatic compounds by Kajigaeshi and his coworkers[19], but it was seldom used for aromatic heterocyclic compounds, with exception of thiophene[20] and acylindole derivatives[21].

We wish to report on the direct selective halogenation of acridine and acridone with benzyltriethylammonium tribromide ( $BTEABr_3$ ), dichloroiodate ( $BTEAICl_2$ ) and tetrachloroiodate ( $BTEAICl_4$ ).

The reaction of acridine **1** and acridone **3** with BTEA polyhalides gave mono- and dihalogenated substituted derivatives **2** and **4**:

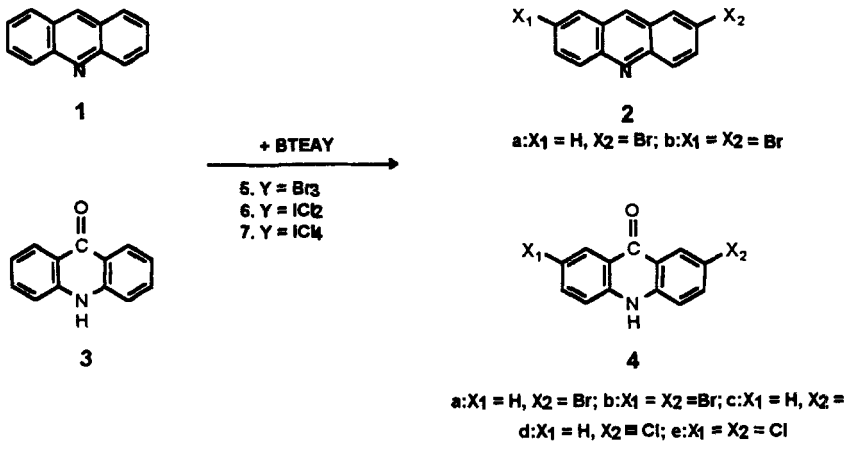

**Table** . Halogenated acridine and acridone derivatives prepared using BTEA polyhalides.

| Compound | $X_1$ | $X_2$ | m. p. (lit. m. p. ) °C | Yield (lit. yield) % |
|---|---|---|---|---|
| **2a** | H | Br | 176 -177 (175[2,18]) | 60 ( 49[2] ) |
| **2b** | Br | Br | 249-250 (252[2,15] ) | 70 ( 55[2] ) |
| **4a** | H | Br | 360 ( 360[5] ) | 60 ( low [1] ) |
| **4b** | Br | Br | >350 ( 438[5] ) | 80 (80[1]) |
| **4c** | H | I | > 350 ( 437[5] ) | 50 - 80 ( 15[5] ) |
| **4d** | H | Cl | > 360 ( > 360[8] ) | 60 (low[5]) |
| **4e** | Cl | Cl | > 350 ( 434[4] ) | 65 (35[4]) |

The result of our experiments are summarized in Table. The halogenation reactions usually proceeded stoichiometrically. However, the reaction of acridine with $BTEAICl_4$ gave a mixture of several chlorosubstituted acridone derivatives, detected by mass spectrometry, due to the fact that the presence of both very reactive species $Cl^+$ and $Cl^-$ into the reaction mixture, leads to the beginning to the formation of mono- and polyhalogenated 9-chloroacridine derivatives which afterwards hydrolysed to corresponding acridone in presence of protic polar solvent ($CH_3OH$). This reaction allowed us to obtain 2,7-dichloroacridone from acridine ( see experimental ).

In the case of bromination and iodination, the use of zinc chloride may leads to complexes with $BTEABr_3$ and $BTEAICl_2$, producing such active species

as $(PhCH_2Et_3N)^+(ZnCl_2Br_2)^{2-}$ $Br^+$ and $(PhCH_2Et_3N)^+(ZnCl_6)^{2-}$ $I^+$ respectively[22]. But in the case of acridine derivatives we noticed that $ZnCl_2$ did not act as a catalyst because acridine forms a complex with this reagent, complex which precipitated out and the reaction did not take place any further.

Our experiments showed that acridine did not undergo electrophilic substitution reactions with $BTEAICl_2$ and $BTEAICl_4$, on the other hand these reagents allowed us to obtain acridine ICl **8** and acridine $ICl_3$ **9** complexes in good yields .

The presence of the methanol as solvent markedly facilitates halogenations because the active species generated are probably methyl hypobromite, hypochlorite or hypoiodite produced by the reaction of BTEA polyhalides with methanol, e.g.:

$$PhCH_2Et_3N^+\ Br_3^- + CH_3OH \longrightarrow PhCH_2Et_3N^+\ Br^- + CH_3OBr + HBr$$

We belive that this procedure for the direct halogenation of acridine and acridone using BTEA polyhalides, stables, solids reagents, is more useful and effective for preparing mono- and dihaloacridine and acridone derivatives, than using molecular chlorine , bromine, iodine or ICl, owing to its ease, simplicity, a better control of reagent - substrate molar ratio and higher yields in comparison with the previous method.

As a limitation to the procedure, due to the fact that these reagents are less reactive but more selective, attempts to prepare tri- and tetra-halogenated acridine and acridone derivatives, valuable from synthetical point of view, were unsuccessful; e.g. the reaction of acridone (1 mmol) with $BTEAICl_4$ (4 mmols) in

methanol under reflux for 35 hours, leads to a mixture which contains equal amounts of di- and trichloroacridone derivatives difficult to separate.

In order to compare our results, with those reported, only yields obtained by direct halogenation of the substrate were considered, because ring closure of diphenylamino-2-carboxylic acid derivatives shows lower general yields.



## EXPERIMENTAL

The elemental analyses for C,H,N and halogen were within +/- 0,4 % of the theoretical values for compounds **4b, 4c, 4d, 4e, 5, 6** and **7** .Melting points are uncorrected. Mass spectra were recorded on a Varian MAT 311 instrument operated at an electron energy of 70 eV. The reactions were monitored by TLC using benzene:ether 4:1 or benzene:ethanol 4:1 (v:v) as eluent, visualisation was done with iodine. BTEA polyhalides were prepared by method given for corresponding benzyltrimethylammonium polyhalides[22,23,24]. The melting points are as follows: compound **5** = 101 - 101 °C, **6** = 79 °C and **7** = ll4 - 128 °C.

**2-Bromoacridine (2a) .** A mixture of acridine ( 0.36 g , 2 mmols ) , $BTEABr_3$ ( 0.9 g , 2 mmols ), acetic acid ( l5 mL ) and methanol ( 5 mL ) was magnetically stirred at room temperature for 8 hrs. Subsequently the precipitate was filtered and washed well with $CH_2Cl_2$ ( see Table ). MS: m/e 257 ($M^+$), 259 ($M^+ + 2$).

**2,7-Dibromoacridine (2b).** A mixture of acridine ( 0.18 g , *l mmol* ), $BTEABr_3$ ( 0.9 g , 2 mmols ) and methanol ( 20 mL ) was stirred at 80 °C on a water bath for 2 hrs, then the reaction mixture was filtered off and the mother liquor concentrated at half in vacuo, filtered hot and the precipitate washed well with

EtOH ( see Table ). MS: m/e 335 ($M^+$), 337 ($M^+ + 2$) and 339 ($M^+ + 4$).

**2-Bromoacridone (4a).** A mixture of acridone ( 0.195 g , 1 mmol ), $BTEABr_3$ ( 0.45g , 1 mmol ) and acetic acid ( 20 mL ) was magnetically stirred at room temperature for 10 hrs. Subsequently the precipitate was filtered and washed with $CH_2Cl_2$ ( see Table ). MS: m/e 273 ($M^+$), 275 ($M^+ + 2$).

**2,7-Dibromoacridone (4b).** A mixture of acridone ( 0.195g , 1 mmol ), $BTEABr_3$ ( 0.9g , 2 mmols ) and acetic acid ( 50 mL ) was stirred at 80°C on a water bath for 8 hrs, then the reaction mixture was filtered hot, the filtrate cooled and the precipitate collected ( see Table ). MS : m/e 351 ( $M^+$ ), 353 ( $M^+ + 2$ ) and 355 ( $M^+ + 4$ ).

**2-Iodoacridone ( 4c ). a/** A mixture of acridone ( 0.195 g , 1 mmol ), $BTEAICl_2$ ( 0.40 g , 1 mmol ), acetic acid ( 30 mL ) and $ZnCl_2$ ( 0.30 g , 2 mmols ) was stirred at 60 °C on a water bath for 1 hr. Subsequently the reaction mixture was cooled, filtered and the precipitate was recrystallized from acetic acid.

**b/** A mixture of acridone ( 0.195g , 1 mmol ), $BTEAICl_2$ ( 0.80 g , 2 mmols ) and acetic acid ( 25 mL ) was stirred at 60 °C on a water bath for 4 hrs. The reaction mixture was worked up as above (see Table). MS : m/e 321 ($M^+$).

**2-Chloroacridone ( 4d ) .** A mixture of acridone ( 0.195 g , 1 mmol ), $BTEAICl_4$ ( 0.460 g , 1 mmol ) and acetic acid ( 20 mL ) was magnetically stirred at room temperature for 10 hrs., then the reaction mixture was cooled, filtered and the precipitate recrystallized from acetic acid ( see Table ). MS : m/e 229 ( $M^+$ ) and 231 ( $M^+ + 2$ ) .

**2,7-Dichloroacridone ( 4e ) .** A mixture of acridine ( 0.18 g , 1 mmol ), $BTEAICl_4$ ( 0.92 g , 2 mmols ) and methanol ( 20 mL ) was stirred at 80°C on a water bath for 1,5 hrs. Subsequently the reaction mixture was cooled, filtered and the precipitate was recrystallized from acetic acid (see Table). MS: m/e 263 ($M^+$ ), 265 ($M^+ + 2$) and 267 ($M^+ + 4$).

**Acridine ICl complex ( 8 ) .** A mixture of acridine ( 0.18 g , 1 mmol ), $BTEAICl_2$ ( 0.80 g , 2 mmols ) and methanol (12 mL ) was magnetically stirred at room temperature for 5 hrs. Subsequently the reaction mixture was then filtered and the precipitate washed well with $CH_2Cl_2$ Yield 60%, m.p. = 177-179 °C ( lit.[25] m.p. = 177 - 178 °C ).

**Acridine $ICl_3$ complex ( 9 ) . a/.** A mixture of acridine ( 0.18 g , 1 mmol ), $BTEAICl_2$ ( 0.40 g , 1 mmol ), acetic acid ( 15 mL ) and $CH_2Cl_2$ ( 5 mL ) was magnetically stirred at room temperature for 17 hrs.Then the precipitate was collected and washed well with $CH_2 Cl_2$ . Yield 100 %.

**b/.** A mixture of acridine ( 0.36 g , 2 mmols ), $BTEAICl_4$ ( 0.92 g , 2 mmols ) and acetic acid ( 15 mL ) was magnetically stirred at room temperature for 9 hrs. The precipitate was collected and worked up as above. Yield 68%, m.p. = 210 - 212 °C ( lit.[25] m.p. = 212 - 213 °C ).

## REFERENCES.

[1]Acheson, R. M., and Robinson, M. J. T., *J. Chem. Soc...*, **1953,** 232.

[2] Acheson, R. M., Hoult, G. T. and Barnard, K. A., *J. Chem. Soc..*, **1954,** 4142.

[3] Ionescu, M. Goia, I, and Felmeri, I., *Studii Cerc. Chim.*, ( Cluj, Romania ), **1957**, *8*, 351; *C. A* , **1960**, *54* , 4587.

[4] Ionescu, M., and Goia, I., *Studii Cerc. Chim.*, ( Cluj, Romania ), **1959**, *10* , 335; *C. A..*, **1961**, *55* , 553.

[5] Goia, I., *Disertation*, **1969**, Cluj, Romania.

[6] Ionescu, M., Goia, I., and Vlassa, M., *Rev. Roumaine Chim.*, **1970**, *15* , 1785.

[7] Ullman, F. and Wagner, C., *Annalen*, **1907**, *355*, 359.

[8] Ullman, F. and Tedesco, E., *Annalen*, **1907**, *355*, 336.

[9] Tănăsescu, I. and Ramonţian, R., *Bull. Soc.Chim. France*, **1934**, *1*, 547.

[10] Grandmougin, E. and Smirous, K., *Ber. deut. chem. Ges.*, **1913**, *46*, 3425.

[11] Lehmsted, E. and Schroder, K., *Ber. deut. chem. Ges.*, **1937**, *70*, 838.

[12] Tănăsescu, I. and Fărcasan, V., *Analele Acad. Române,Ser., A2*, **1949**, *16* , 24; *C. A.*, **1952**, *46*, 8118.

[13] Albert, A. and Rayer, R., *J. Chem. Soc.*, **1949**, 1148.

[14] Singh, S. and Singh, M., *J. Sci. Res .*, ( India ), **1951**, *10 B* , 180, 298 ; *C.A .*, **1954**, *48* , 4547, 8785.

[15] Kliegel, A. and Schaible, L., *Chem. Ber.*, **1957**, *60*, 90.

[16] Tănăsescu, I. and Frenkel, Z., *Bull. Soc. Chim. France*, **1960**, 693.

[17] Tănăsescu, I., Fărcasan, V. and Piringer, O., *Studii Cerc. Chim.*, ( Cluj, Romania ), **1961**, *12*, 285; *C. A.*, **1963**, *59*, 573.

[18] Chandler, R., Jones, A. and Sasse, W. H. F., *Austral. J. Chem .*, **1965**, *18*, 108.

[19] Kajigaeshi, S., Kakinami, T., Okamoto, T., Nakamura, H. and Fujikawa, M., *Bull. Chem. Soc. Jpn.*, **1987**, *60*, 4187.

[20] Okamoto, T., Kakinami, T., Fujimoto, H. and Kajigaeshi, S., Bull.,*Chem. Soc. Jpn.*, **1991**, *64*, 2566.

[21] Preobrazhenskaia, M.N., Orlova, L. M. and Suvorov, N. N.*Zh. Vses. Khim. Obshchest.*, **1968**, *13*, 246; *C. A.*, **1968**, *69*, 86748.

[22] Kajigaeshi, S., Kakinami, T., Moriwaki, M., Tanaka, T., Fujisaki, S. and Okamoto, T., *Bull. Chem. Soc. Japan .*, **1989,** *62*, 439.

[23] Kajigaeshi, S., Kakinami, T., Moriwaki, M., Fujisaki, S., Maeno, K. and Okamoto, T., *Synthesis,* **1988,** 545.

[24] Kajigaeshi, S., Kakinami, T., Ikeda, H., Okamoto, T., *Chemistry Express,* **1988**, *3*, 659.

[25] Whitaker, R. D., *J. Inorg. Nucl. Chem.*, **1964,** *26*, 439.

(Received in The Netherlands 05 April 1995)