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Tetrahalogenomethanes: simple reagents for the synthesis of monohalogenated and mixed dihalogenated aromatic heterocycles via metal–halogen exchange from lithium compounds

Carla Boga *, Erminia Del Vecchio, Luciano Forlani, Paolo Edgardo Todesco

Dipartimento di Chimica Organica 'A. Mangini', via le Risorgimento, I-40136 Bologna, Italy

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Abstract

Tetrabromo- or tetrachloromethane and 2-lithio derivatives of aromatic heterocycles rapidly produce the corresponding 2-bromo or 2-chloro derivatives in high yields through a metal–halogen exchange mechanism. This kind of reaction was also used to obtain, in good yields, 5-bromo-2-chlorothiazole and 5-bromo-2-chloro-*N*-methylimidazole. © 2000 Elsevier Science S.A. All rights reserved.

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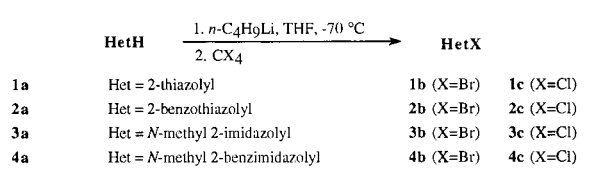
1. Introduction

Haloderivatives of thiazole, imidazole and their benzocondensates are of wide importance in organic chemistry as intermediates in the synthesis of many compounds, most of them of biological interest.

Classical methods to obtain aromatic haloderivatives [1], such as the Sandmeyer reaction or direct halogenation, often require tedious or drastic conditions, even if the Sandmeyer reaction on 2-aminothiazoles remains the preferred route to obtain the corresponding 2-halo derivatives (with yield depending on the substituents on the ring [2a]) because of the inexpensive starting material [2b]. The direct halogenation of thiazole and *N*-alkyl imidazoles affords mixtures of mono-, di- or trihalogenated derivatives [3], and benzothiazole is brominated in the 2-position only under drastic reaction conditions. In addition, these methods are not suitable for the preparation of mixed polyhalo derivatives and only a few syntheses of mixed dihaloderivatives of thiazole [4] and imidazole [5] have been reported so far. An alternative route is the regioselective metallation of the heterocycle, followed by treatment with different halogen sources [1,6]; in this context we recently found [7] that 2-chloro derivatives of thiazole, *N*-methylimidazole and their benzo analogues can be easily obtained, in good yield, via metal–halogen exchange reaction between 2-lithio precursors and trichloroacetyl compounds.

These findings prompted us to perform this reaction using tetrahalogenomethanes, the reactivity of which with magnesium or lithium compounds has been extensively studied [8], but scarcely used for the present synthetic purpose [9].

Now we report results showing that tetrahalogenomethanes are useful 'positive halogen ion' donors for performing a simple, efficient and regiospecific halogenation of heterocycles.



Scheme 1.

* Corresponding author. Tel.: +39-051-2093616; fax: +39-051-2093654.

E-mail address: boga@ms.fci.unibo.it (C. Boga)

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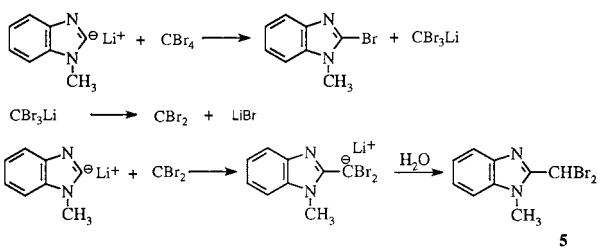
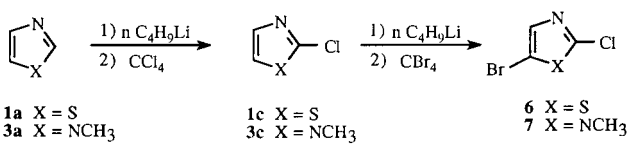
Table 1
Reactions between 2-lithio derivatives of heterocycles **1a**–**4a** and tetrahalogeno methanes [a]

Entry	HetH	CX_4	Reaction time (min)	Product (yield %)
1	**1a**	CBr_4	15	**1b** (80) [b]
2	**1a**	CCl_4	30	**1c** (90) [b]
3	**2a**	CBr_4	15	**2b** (80) [c], (75) [d]
4	**2a**	CCl_4	15	**2c** (90) [b]
5	**2a**	$CBrCl_3$	30	**2b** (35) [d,e] **2c**(7) [d,e]
6	**3a**	CBr_4	15	**3b** (80)[c]
7	**3a**	CCl_4	15	**3c** (75) [b]
8	**4a**	CBr_4	15	**4b** (65) [b,f]
9	**4a**	CCl_4	15	**4c** (85) [b], (76)[d]

[a] Reactions carried out in anhydrous THF, at −70°C.
[b] Yield from GC–MS.
[c] Conversion calculated from ^{1}H-NMR spectra.
[d] Yield from FC.
[e] 30% of **2a** was recovered.
[f] 10% of 2-(dibromomethyl)-*N*-methylbenzimidazole (**5**) was also recovered.



Scheme 2.



Scheme 3.

2. Results and discussion

The reaction between the 2-lithio derivative of thiazole (**1a**), benzothiazole (**2a**), *N*-methylimidazole (**3a**) and *N*-methylbenzimidazole (**4a**) and an equimolar amount of tetrabromomethane or tetrachloromethane (Scheme 1) was performed in THF at −70°C to give, in a few minutes, the corresponding haloderivative in good yield (Table 1).

The reported results show that the metal–halogen exchange occurs immediately, giving the chlorinated and the brominated products in good yields. In the case of the reaction between 2-lithio-*N*-methylbenzimidazole and tetrabromomethane, we also isolated 10% of 2-(dibromomethyl)-*N*-methylbenzimidazole (**5**), probably deriving from a side reaction between 2-lithio-*N*-methylbenzimidazole and dibromocarbene, which arises from lithio-tribromomethane, according to Scheme 2.

When bromotrichloromethane was used, a mixture of both bromo- and chloro-derivatives was obtained, in which the brominated product predominated (5:1).

The results obtained above prompted us to use this simple and direct halogenation method to synthesize mixed dihaloderivatives of thiazole and *N*-methylimidazole, the syntheses of which have been reported in few cases.

2-Chloro-5-bromothiazole (**6**) and 2-chloro-5-bromo-*N*-methylimidazole (**7**) were obtained as depicted in Scheme 3.

Thiazole (**1a**) and *N*-methylimidazole (**3a**) were metallated with *n*-butyl lithium at −70°C and then treated with tetrachloromethane to give the corresponding 2-chloro derivatives. A successive treatment with *n*-butyl lithium, followed by addition of CBr_4, gave the mixed dihalogenoderivatives **6** and **7** in satisfactory yields.

All the products were characterized by ^{1}H-, ^{13}C-NMR and MS spectrometry. The structure of compound **7** was ascertained by ^{1}H–^{1}H NOE experiments.

In conclusion, chlorination and bromination of aromatic azaheterocycles can be easily performed via metal–halogen exchange between lithio precursors and tetrahalogenomethanes. This can be considered as a simple and efficient alternative to classical methods for obtaining chloro and bromo heterocycles regioselectively.

3. Experimental

3.1. General

^{1}H, ^{1}H–^{1}H NOE and ^{13}C-NMR spectra were recorded on a Varian Gemini spectrometer at 300 and 75.46 MHz, respectively, in $CDCl_3$ ($\delta = 7.27$ ppm for ^{1}H-NMR and 77.20 ppm for ^{13}C-NMR). *J* values are given in Hz. IR spectra were recorded on a Perkin–Elmer spectrophotometer model 1600 FTIR. MS spectra were recorded at an ionization voltage of 70 eV on a VG 7070 E spectrometer. GC–MS analyses were performed on a HP-5890 gas chromatograph equipped with a methyl silicone capillary column and an HP-5970 mass detector. Chromatographic purifications were carried out on columns packed with silica gel Kieselgel (Merck, 230–400 mesh) at medium pressure. Thin-layer chromatography was performed on Merck Kieselgel 60 F_{254}. Melting points were measured with a Büchi apparatus and are uncorrected. THF was distilled from sodium benzophenone ketyl. All of the reagents were commercial samples (Aldrich). All the reactions were performed in a flame-dried apparatus under a static atmosphere of dry nitrogen. 2-Lithio derivatives of compounds **1a**–**4a** were prepared as in

Ref. [3]. The characteristics of compounds **1b**, **1c**, **2c**, **3c**, **4c** are in agreement with literature data [7,10].

3.2. Reactions between 2-lithio heterocycles and tetrahalogenomethanes: typical procedure

To a solution containing 2.5 mmol of 2-lithio-*N*-methyl benzimidazole in 5 ml of THF, cooled at −70°C, CCl_4 (0.24 ml, 2.5 mmol) (diluted in 5 ml of THF) was added. The solution turned immediately dark and after 15 min, TLC (eluant: 7:3 light petroleum–diethyl ether) and GC–MS analyses showed 85% conversion. After 15 min, the reaction was quenched with a saturated aqueous solution of NH_4Cl (2 ml), diluted with diethyl ether and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed at reduced pressure. FC (eluant: dichloromethane) of the residue gave 0.315 g (76%) of **4c**.

3.3. Physical constants of compounds synthesized

3.3.1. 2-Bromobenzothiazole (**2b**)

M.p. 39–41°C (lit. [11]: 39.5–40°C). ^{1}H-NMR ($CDCl_3$): δ 7.98 (dd, 1H, $J = 7.5$, $J = 1.5$ Hz, 4-H or 7-H), 7.79 (dd, 1H, $J = 7.8$, $J = 1.8$ Hz, 4-H or 7-H), 7.50–7.35 (m, 2H, 5-H and 6-H). ^{13}C-NMR ($CDCl_3$): δ 152.5, 139.0, 137.5, 126.8, 126.0, 123.0, 121.0. MS (*m*/*e*): 215, 213, 134.

3.3.2. 2-Bromo-N-methylimidazole (**3b**)

^{1}H-NMR ($CDCl_3$): δ 6.85 (d, 1H, $J = 2.1$ Hz), 6.72 (d, 1H, $J = 2.1$ Hz), 3.40 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): δ 129.0, 122.8, 119.4, 34.2.

3.3.3. 2-Bromo-N-methylbenzimidazole (**4b**)

M.p. 102–104°C (lit. [12]: 103–105°C). ^{1}H-NMR ($CDCl_3$): δ 7.72–7.65 (m, 1H, aromatics), 7.30–7.20 (m, 3H, aromatics), 3.75 (s, 3H, NCH_3). ^{13}C-NMR ($CDCl_3$): δ 142.9, 136.0, 130.4, 123.2, 122.6, 119.2, 109.3, 31.7. MS (*m*/*e*): 212 [$M^+ + 2$], 210 [M^+], 129, 104.

3.3.4. 2-(Dibromomethyl)-N-methylbenzimidazole (**5**)

^{1}H-NMR ($CDCl_3$): δ 7.80–7.72 (m, 1H, aromatics), 7.39–7.31 (m, 3H, aromatics), 6.96 (s, 1H, $CHBr_2$), 4.05 (s, 3H, NCH_3). ^{13}C-NMR ($CDCl_3$): δ 148.5, 139.6, 136.7, 124.7, 123.6, 120.5, 109.7, 31.6, 27.9. MS (*m*/*e*): 304 [$M^+ + 2$], 302 [M^+], 225, 223, 212, 210, 129. HRMS: $C_9H_8Br_2N_2$ requires: 301.9054. Found: 301.9049.

3.3.5. 5-Bromo-2-chlorothiazole (**6**)

A solution of 2-chlorothiazole **1c** (0.18 g, 1.48 mmol, in 5 ml of THF) was cooled at −70°C. After 15 min, a 2.5 M solution of *n*-BuLi (0.6 ml, 1.48 mmol) in *n*-hexane, diluted with 2 ml of anhydrous THF, was slowly added. After further 30 min, CBr_4 (0.48 g, 1.48 mmol), dissolved in THF (2 ml), was added. The reaction was monitored by TLC (eluant: 7:3 petroleum light–diethyl ether) and GC–MS analyses, then it was quenched with aqueous saturated solution of NH_4Cl, diluted with diethyl ether, and dried over anhydrous Na_2SO_4. After filtration, evaporation of the solvent at reduced pressure and FC (eluant: 7.5:2.5 light petroleum–diethyl ether) of the residue, pure **6** (0.08 g, 27%) was obtained.

^{1}H-NMR ($CDCl_3$): δ 7.51 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 145.4, 142.8, 109.3. MS (*m*/*e*): 201 [M^+], 199, 197, 120, 118.

3.3.6. 5-Bromo-2-chloro-N-methylimidazole (**7**)

compound **7** was obtained in 63% yield from **3c** following the procedure above described for the preparation of **6**.

M.p. 92–94°C. ^{1}H-NMR ($CDCl_3$): δ 6.92 (s, 1H), 3.59 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): δ 131.9, 128.1, 103.7, 32.2. MS (*m*/*e*): 198 [M^+], 196, 194, 117, 115, 80.

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