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A new synthesis of chloroheterocycles via metal–halogen exchange between trichloroacetyl derivatives and heteroaromatic lithium and Grignard reagents

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Abstract

The reaction between 2-lithio derivatives of aromatic azaheterocycles and trichlorocetyl derivatives rapidly produces the corresponding 2-chloro derivatives in high yields through a metal–halogen exchange mechanism. The use of ethyl trichloroacetate can give better results with respect to those obtained with trichloroacetyl chloride, which probably involves dichloroketene formation. The reaction with Grignard reagents is more complex: in fact, 2-benzothiazolylmagnesium chloride with ethyl trichloroacetate or trichloroacetyl chloride gives 2-chlorobenzothiazole together with considerable amounts of ethyl 1,3-benzothiazole-2-carboxylate or 2-benzothiazolyl dichloromethyl ketone, respectively.

Keywords: Chlorination; Trichloroacetyl chloride; Grignard reagents; Lithium compounds; Aromatic heterocycles; Metal–halogen exchange

1. Introduction

Haloderivatives of heterocycles like thiazoles, oxazoles, imidazoles and their benzoderivatives are interesting compounds as useful intermediates for the preparation of a wide number of substances, most of these of biological interest. Classical methods to obtain these compounds [1], such as the Sandmeyer reaction on aminoprecursors or the direct halogenation under drastic conditions, are often laborious and limited in yield and, in the latter case, in regioselectivity. For example, 1,3-imidazoles, 1,3-oxazoles and 1,3-thiazoles suffer electrophilic attack at either the 5 or a combination of both 4 and 5 positions, whereas benzimidazoles and benzothiazoles also undergo electrophilic substitution in the benzenoid moiety of the molecule [1,2]. Alternatively, the metalation of these compounds occurs exclusively in position 2 and several derivatives have been obtained after treatment with electrophiles, but very few examples of synthesis of chloroderivatives via metal–chlorine exchange from lithium compounds or Grignard reagents have been reported so far [3].

In the literature, some reactions involving metal–halogen exchange in which trichloroacetyl derivatives were used as 'positive chloro ion' donors have been reported: the reaction between isopropylmagnesium chloride and ethyl trichloroacetate was exploited to produce, in high yield, the corresponding dichloroacetyl enolate [4], whereas 2-thienyl-lithium reacts with trichloroacetonitrile to give 2-chlorothiophene in 40% yield [5].

These findings prompted us to perform the reaction between lithium and Grignard derivatives of some azaaromatics and trichloroacetyl derivatives, in order to check if it was possible to obtain the corresponding chloroheterocycles by a simple and direct procedure.

Here we report the obtained results which, in the case of the reaction between 2-benzothiazolylmagnesium chloride and trichloroacetyl derivatives, are unexpected and allow us to propose a reaction mechanism.

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2. Results and discussion

The reaction (Scheme 1) between 2-benzothiazolylmagnesium chloride (**2**) (prepared from benzothiazole (**1**) and ethylmagnesium chloride) and ethyl trichloroacetate (**3**) (1:1 molar ratio) afforded a mixture of products, with prevalence of 2-chlorobenzothiazole (**4**) (57%) and ethyl 1,3-benzothiazole-2-carboxylate (**5**) (25%), coming from an attack to carboxylic carbon followed by elimination of trichloromethyl anion.

This fact allowed us to perform the reaction between **2** and trichloroacetyl chloride (**6**), bearing a better leaving group than **3**, in order to increase the yield of **4**.

The reaction (Scheme 2) was carried out at 0°C with equimolar amount of **2** respect to **6** (Table 1, entry 1).

After about 10 min, the GC–MS analysis of the reaction mixture revealed the presence of several products, some of them identified as **4** (62%), 2-benzothiazolyl dichloromethyl ketone (**7**) (18%) and 2-benzothiazolyl trichloromethyl ketone **8** (20%). The structure of products was ascertained by spectroscopic analyses of isolated compounds and/or by comparison with authentic samples (see Section 3).

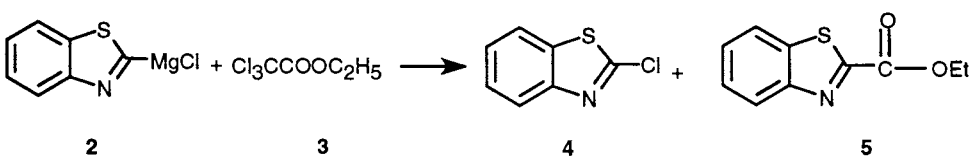
The recovery of both **4** and **8** is due to the competition between the two reactive groups — trichloromethyl and carbonyl — present on **6**: 2-chlorobenzothiazole (**4**) arises from a halogen–metal exchange reaction between **2** and the trichloromethyl group, whereas **8** comes from the usual 1,2 attack to carbonyl group. The 'positive chloro ion' extraction might occur through a pathway involving the formation of dichloroketene, favored by the departure of a good leaving group such as the chloride ion (Scheme 3).

The presence of **7** in the reaction mixture supports this mechanism because the dichloroketene could react with the remaining Grignard reagent **2** to give an enolate that, after quenching, tautomerizes to the stable form **7**. Since **4** and **7** can also arise from a halogen–metal exchange between **2** and **8**, we performed the reaction between these reagents in THF at 0°C, but we found neither **4** nor **7** in the reaction mixture: this result agrees with the proposed mechanism of Scheme 3.

The reaction depicted in Scheme 2 was carried out in THF under different experimental conditions; the results obtained are collected in Table 1.

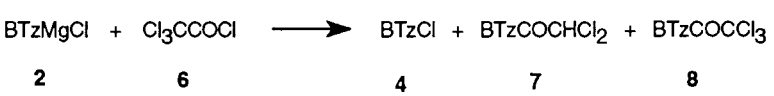
Reactions carried out at 0°C and at room temperature were immediate and gave mixtures of products with prevalence of **4**. At room temperature, only 2-chlorobenzothiazole (**4**) and ketone **7** were recovered. When an excess of organometallic reagent was used (entry 3), a small amount of bis(2-benzothiazole) (**9**) was detected.

Lowering the reaction temperature to −70°C, a low reactivity and an increase in the yield of addition product **8**, with respect to **4** and **7**, were observed (entry 4); after 24 h, the temperature being allowed to stand, many unidentified by-products were present in the reaction mixture.



2 **3** **4** **5**

Scheme 1.



2 **6** **4** **7** **8**

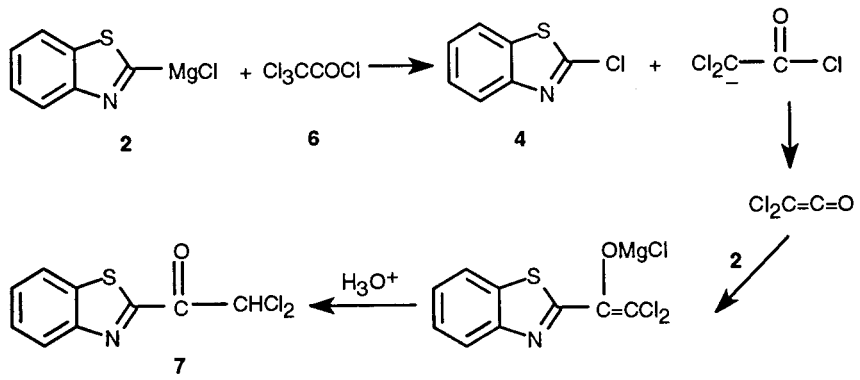
BTz = 2-benzothiazolyl

Scheme 2.

Table 1
Reaction between **2** and **6**

Entry	Molar ratio	Reaction		Products[a]				
	2:**6**	Temperature (°C)	Time	**1**	**4**	**7**	**8**	**9**
1	1:1	0	10 min	–	62	18	20	–
2	1:1	r.t.	10 min	–	75	25	–	–
3	2:1	0 to r.t.	30 min	–	69	16	3	6
4	2:1	−70 to −10	4 h	62	16	4	18	tr.

[a] Relative ratio from GC–MS analysis.



Scheme 3.

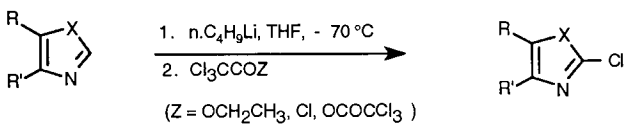
These data clearly indicate that the temperature plays an important role in driving the regiochemistry of the attack towards the 1,2 addition to carbonyl group or the metal–halogen interchange. In addition, the data reported above show that the reactions between the Grignard reagent **2** and trichloroacetyl derivatives were unpredictable: it should be noted that the use of the ester or of the acyl chloride generates different behaviors, with formation of different by-products.

This fact prompted us to perform the reaction between trichloroacetyl derivatives and 2-lithio derivatives, to increase the yield of metal–halogen interchange product and to avoid side reactions (Scheme 4).

Reactions between 2-lithiobenzothiazole (**10**) and trichloroacetyl derivatives were carried out in THF at − 70°C, with different molar ratios of the reagents. The obtained results are shown in Table 2, together with those from the reactions between lithium derivatives of heterocycles **11**, **13**, **15**, **17** and trichloroacetylchloride.

The reactions gave, after a few minutes, 2-chloroheterocycles in satisfactory yield: this chlorinating method is better than classical methods [1].

2-Lithiobenzothiazole (**10**) gave quantitatively the metal–chlorine exchange product **4**, also using the trichloroester **3** or the trichloroacetic anhydride (entries 1–3). The better result obtained using ethyl trichloroacetate with respect to the use of trichloroacetyl chloride can be explained considering that, with the latter



1	R-R' = C_4H_4	X = S	**4**
11	R, R' = H	X = S	**12**
13	R-R' = C_4H_4	X = O	**14**
15	R-R' = C_4H_4	X = NCH_3	**16**
17	R, R' = H	X = NCH_3	**18**

Scheme 4.

reagent, the formation of the very reactive dichloroketene may interfere. Consequently, the behavior of ethyl trichloroacetate could be generalized, making it an easy reagent for synthetic purposes. When an excess of **10** was used (entries 4, 5), **4** was obtained together with a considerable amount of **9** and only traces of **7**, detectable in GC–MS analysis.

For comparison, we also performed the reaction between 2-lithiobenzothiazole (**10**) and *N*-chlorosuccinimide: after 1 h at − 70°C the GC–MS analysis of the reaction mixture showed conversion to **4** in 68% yield. In the case of *N*-methylimidazole (**17**) the reaction afforded the corresponding chloroderivative in better yield with respect to that reported in a similar reaction with *N*-chlorosuccinimide as chlorinating agent [6]. The low yield obtained in the case of 2-chlorobenzoxazole (**14**) is probably due to the low stability of the 2-lithio precursor, which is in equilibrium with its opened form [7].

In conclusion, the reaction between the Grignard reagent **2** and trichloroacetyl derivatives gave a mixture of products from different reaction pathways, whereas using the corresponding lithium derivative **10** a complete regioselectivity toward the 'positive halogen ion' extraction was observed. This reaction was also extended to other heterocycles, giving the corresponding chloroderivatives in good yields. This method can be considered an efficient non-classical halogenation route to chloroheterocycles.

3. Experimental

3.1. General

^{1}H- 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 model 1600 FT-IR spectrophotometer. MS spectra were recorded at

Table 2
Reactions between lithio heterocycles and Cl_3CCOZ[a]

Entry	Heterocycle	Cl_3CCOZ	Molar ratio	Reaction time	Product (yield %)
1	**1**	$Cl_3CCOOEt$	1/1	30 min	**4** (94[b,c])
2	**1**	$(Cl_3CCO)_2O$	1/1	30 min	**4** (95[b,c])
3	**1**	Cl_3CCOCl	1/1	30 min	**4** (75[d], 82[b,c])
4	**1**	Cl_3CCOCl	2/1	20 min	**4** (50[d])
5	**1**	Cl_3CCOCl	3/1	180 min	**4** (50[c,e])
6	**11**	Cl_3CCOCl	1/1	30 min	**12** (87[f])
7	**13**	Cl_3CCOCl	1/1	72 h	**14** (20[c], 15[d])
8	**15**	Cl_3CCOCl	1/1	30 min	**16** (90[d])
9	**17**	Cl_3CCOCl	1/1	30 min	**18** (70[c,f])

[a] Reactions carried out in anhydrous THF, at −70°C.
[b] Conversion.
[c] Yield from GC–MS.
[d] Yield from FC.
[e] In this case also 30% of bis(2-benzothiazole) (**9**) was recovered.
[f] Conversion calculated from ^{1}H-NMR spectra.

an ionization voltage of 70 eV on a VG 7070 E spectrometer. GC–MS analyses were performed on an 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 the reagents were commercial samples (Aldrich). Ethylmagnesium chloride was from Aldrich and was titrated immediately before use by standard methods [8]. All the reactions were performed in a flame-dried apparatus under a static atmosphere of dry nitrogen. 2-Benzothiazolylmagnesium chloride **2** was prepared according to the procedure [9] described for the preparation of 2-thiazolylmagnesium bromide. 2-Lithio derivatives were prepared as in ref. [2]. Authentic samples of 2-benzothiazolyl dichloromethyl ketone (**7**) and 2-benzothiazolyl trichloromethyl ketone (**8**) were synthesized from 2-(trimethylsilyl)-benzothiazole and the respective acyl chloride, according to literature procedures [10,11].

3.2. Reactions between **2** and trichloroacetyl derivatives: typical procedure

To a solution of **2** (2.5 mmol in 10 ml of THF), cooled at 0°C, a solution of ethyl trichloroacetate (**3**) (2.5 mmol in 5 ml of THF) was added. The reaction was monitored by TLC and GC–MS analyses. When the spot (or the peak) corresponding to benzothiazole (**1**) disappeared, the reaction mixture was treated with saturated aqueous solution of NH_4Cl. After extractions with diethyl ether and CH_2Cl_2, the organic layers were washed with brine and dried over anhydrous Na_2SO_4 The solvents were removed in vacuum. Flash-chromatography of the residue (eluant: 4:1 light petroleum–diethyl ether) gave 0.241 g (57%) of 2-chlorobenzothiazole (**4**), and 0.130 g (25%) of ethyl 1,3-benzothiazole-2-carboxylate (**5**).

3.3. Reactions between 2-lithio heterocycles and trichloroacetyl derivatives: typical procedure

To a solution of 0.35 ml (5.0 mmol) of thiazole (**11**) in 5 ml of THF, at −70°C, 2.5 ml of *n*-BuLi (2.5 M in *n*-hexane, diluted with 3.0 ml of THF), were added. After 15 min, 0.56 ml (5.0 mmol) of **6** in 3 ml of THF were dropped into the orange solution.

After 30 min the reaction was quenched in saturated aqueous solution of NH_4Cl. After extraction with Et_2O the organic layer was washed with brine, dried over Na_2SO_4 and concentrated at reduced pressure. ^{1}H-NMR spectra of the residue showed the presence of **11** and **12** in 13:87 relative ratio.

3.4. Characteristics of obtained compounds

3.4.1. 2-chlorobenzothiazole (**4**)

^{1}H-NMR ($CDCl_3$), δ 7.91 (dd, 1H, $J = 8.0$ Hz, $J = 0.6$ Hz, 4-H), 7.71 (dd, 1H, $J = 8.0$ Hz, $J = 0.7$ Hz, 7-H), 7.44 (t, 1H, 5-H), 7.38 (t, 1H, 6-H); ^{13}C-NMR ($CDCl_3$), δ 153.0, 150.7, 135.9, 126.4, 125.5, 122.8, 120.9; MS: (m/e) 171, 169, 134.

3.4.2. Ethyl 1,3-benzothiazole-2-carboxylate (**5**)

M.p.:70–71°C (from methanol), lit. [12]: 71°C; ^{1}H-NMR ($CDCl_3$), δ 8.30–8.25 (m, 1H, 4-H or 7-H), 8.02–7.97 (m, 1H, 4-H or 7-H), 7.60 (td, 1H, $J = 7.2$ Hz, $J = 1.6$ Hz, 5-H or 6-H), 7.55 (td, 1H, $J = 7.2$ Hz, $J = 1.4$ Hz, 5-H or 6-H), 4.58 (q, 2H, $J = 7.1$ Hz, CH_2), 1.50 (t, 3H, CH_3). ^{13}C-NMR ($CDCl_3$), δ 160.6, 158.5,

153.2, 136.7, 127.5, 127.0, 125.5, 122.0, 63.1, 14.3. MS: (m/e) 207 [M^+], 162, 135. IR($CHCl_3$) ν: 1735 cm^{-1}.

*3.4.3. 2-Benzothiazolyl dichloromethyl ketone (**7**)*

M.p.: 117–118°C (from methanol); lit. [10]: 118°C. ^{1}H-NMR ($CDCl_3$), δ 8.25–8.21 (m, 1H, 4-H or 7-H), 8.04–8.00 (m, 1H, 4-H or 7-H), 7.67–7.58 (m, 2H, 5-H and 6-H), 7.44 (s, 1H, $CHCl_2$). ^{13}C-NMR ($CDCl_3$), δ 181.1, 161.0, 153.3, 138.2, 128.9, 127.8, 126.2, 122.7, 66.1. MS (m/e): 245, 247, 162, 134. IR ($CHCl_3$): 1720 cm^{-1}.

*3.4.4. 2-Benzothiazolyl trichloromethyl ketone (**8**)*

M.p.: 84.5–86.6°C (from methanol). ^{1}H-NMR ($CDCl_3$), δ: 8.33–8.29 (m, 1H, 4-H or 7-H), 8.06–8.02 (m, 1H, 4-H or 7-H), 7.67–7.61 (m, 2H, 5-H and 6-H). ^{13}C-NMR ($CDCl_3$), δ 175.4, 157.8, 153.4, 137.6, 128.8, 127.6, 126.4, 122.1, 93.5; HRMS: $C_9H_4Cl_3NOS$ requires 278.9072; found: m/e 278.9079; IR ($CHCl_3$) ν: 1712 cm^{-1}.

*3.4.5. Bis(2-benzothiazole) (**9**)*

^{1}H-NMR ($CDCl_3$), δ: 8.90 (d, 2H, $J = 8.8$ Hz), 8.00 (d, 2H, $J = 7.2$ Hz), 7.60–7.42 (m, 4H). MS (m/e): 268 [M^+], 134, 108.

*3.4.6. 2-Chlorothiazole (**12**)*

^{1}H-NMR ($CDCl_3$), δ: 7.59 (d, 1H, $J = 3.7$ Hz, H-4), 7.28 (d, 1H, $J = 3.7$ Hz, H-5). ^{13}C-NMR ($CDCl_3$), δ: 151.9, 141.5, 121.3. MS (m/e): 121, 119, 84.

*3.4.7. 2-Chlorobenzoxazole (**14**)*

^{1}H-NMR ($CDCl_3$), δ: 7.67 (dd, 1H, $J = 6.1$ Hz, $J = 3.2$ Hz), 7.50 (dd, 1H, $J = 6.1$ Hz, $J = 3.6$ Hz), 7.40–7.33 (m, 2H). ^{13}C-NMR ($CDCl_3$), δ: 151.8, 151.1, 141.3, 125.6, 125.2, 119.9, 110.5. MS (m/e): 155, 153, 125, 90, 63.

*3.4.8. 2-Chloro-1-methyl benzimidazole (**16**)*

M.p.: 115–116°C (from light petroleum); lit. [13]: 114–116°C. ^{1}H-NMR ($CDCl_3$), δ 7.70–7.60 (m, 1H, 4-H), 7.30–7.18 (m, 3H, 5-H, 6-H, 7-H), 3.73 (s, 3H, NCH_3). ^{13}C-NMR ($CDCl_3$), δ 141.5, 140.8, 135.5, 123.0, 122.5, 119.2, 109.2, 30.4. MS (m/e): 168, 166, 131, 129.

*3.4.9. 2-Chloro-1-methyl imidazole (**18**)*

^{1}H-NMR ($CDCl_3$), δ: 6.94 (d, 1H, $J = 1.4$ Hz), 6.86 (d, 1H, $J = 1.4$ Hz), 3.57 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$), δ: 131.0, 126.7, 121.4, 32.3. MS (m/e): 118, 116, 89.

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