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REACTIONS BETWEEN HETEROAROMATIC HALIDES AND LITHIUM DIMETHYLCUPRATE; SYNTHETIC AND MECHANISTIC ASPECTS

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Summary

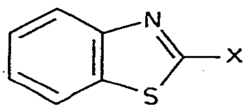
The reactions of halo-benzothiazoles, -pyridines and -benzofurazans with lithium dimethylcuprate have been investigated. Metal—halogen exchange usually occurs together with cross-coupling. The amount of the product derived from the latter process is increased by adding methyl iodide to the reaction mixtures. The significance of the results is discussed.

Introduction

Lithium dialkyl- and diaryl-cuprates are known to be useful reagents for C—C bond formation [1]. Addition and substitution reactions can take place in various systems. Many organic halides of the alkyl, aryl, allyl, vinyl and acyl type react with cuprate with carbon—carbon coupling, which is frequently accompanied by metal—halogen exchange [1,2].

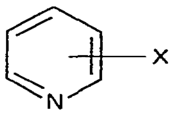
Examples of reactions between heteroaromatic halides and the above reagents are rare [3] and no relevant information is available on the mechanism(s) of these processes. Therefore, in connection with work on similar reactions involving vinylic halides as substrates [4], we have undertaken a study of the reactions of lithium dimethylcuprate with three kinds of typical activated heteroaromatic compounds, viz. I—III.

I



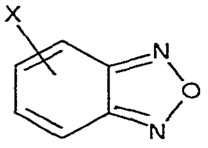
2-Halobenzothiazoles
(2-BT-X , X = F, Cl, I)

II



Halopyridines
(Py-X, X = F, Cl, Br, I)

III



Halobenzofurazans
(BF-X, X = I)

Results and discussion

Reactions of 2-halobenzothiazoles (I)

(a) Reactions with Me_2CuLi. 2-Fluoro-, 2-chloro- and 2-iodo-benzothiazoles were treated with Me_2CuLi in ether at 0° C under an argon stream. In all cases the unsubstituted benzothiazole (BT-H) was obtained in high yield, as shown in Table 1. The iodide was found to be much more reactive than the other halides. In the case of the iodo- compound the formation of the coupling product was also observed both when methyl iodide was added after a suitable time to the reaction mixture or when molecular oxygen was bubbled into the latter [2]. On the other hand, 2-deuteriobenzothiazole was formed in high yield when the reaction between the 2-iodo derivative and Me_2CuLi was quenched with DCl in D_2O.

(b) Reactions with MeLi in ether. We examined the reactions of 2-halobenzothiazoles with methyllithium in order to ascertain the difference of behaviour, if any, between the two types of organometallic reagents. The 2-fluoro derivative was found to react with MeLi giving 2-methylbenzothiazole in 90% yield. On the other hand the 2-iodo derivative gave the unsubstituted benzothiazole.

(c) Reactions with PhLi and Ph_2CuLi in ether. The behaviour of the 2-iodobenzothiazole was investigated. The reaction with PhLi or Ph_2CuLi was rapid, and gave benzothiazole in high yield together with iodobenzene and biphenyl [2a]. The reactions with PhLi and Ph_2CuLi under the same conditions required shorter times than those used for MeLi and Me_2CuLi.

TABLE 1

REACTIONS OF 2-HALOBENZOTHIAZOLES, HALOPYRIDINES AND HALOBENZOFURAZANS (I—III) WITH LITHIUM DIMETHYLCUPRATE IN DIETHYL ETHER AT 0° C

Substrate	Concentration (M × 10)		Reaction times	% Products			Quenching agent
	Substrate	Reagent		Substitution	Reduction	Unreacted	
2-F-BT	0.41	0.45	6 h	—	60	40	HCl 1/1
2-F-BT [a]	0.41	0.45	15 min	90	— [b]	—	HCl 1/1
2-Cl-BT	0.35	0.39	6 h	—	70	30	HCl 1/1
2-I-BT	0.35	0.39	45 min	—	100	—	HCl 1/1
2-I-BT	0.35	0.39	45 min	30	45	—	MeI
2-I-BT	0.35	0.39	1 h	20	—	—	O_2
2-I-BT [a]	0.35	0.39	15 min	—	100	—	HCl 1/1
2-I-BT [a]	0.35	0.39	15 min	60	30	—	MeI
2-F-Py	0.60	2.40	9 h	—	—	100	HCl 1/1
2-Cl-Py	0.60	2.40	9 h	—	—	100	HCl 1/1
2-Br-Py	0.46	1.84	3 h	40	40	15	HCl 1/1
2-I-Py	0.49	1.96	3 h	50	50	—	HCl 1/1
2-I-Py	0.58	0.64	8 h	85	15	—	HCl 1/1
3-I-Py	0.60	0.66	6 h	—	80	20	HCl 1/1
3-I-Py	0.58	2.40	1.5 h	— [b]	—	—	MeI
4-I-BF [c]	0.28	0.85	10 min	—	100	—	HCl 1/1
4-I-BF [c]	0.28	0.85	10 min	60	30	—	MeI
5-I-BF [c]	0.50	1.46	15 min	15	85	—	HCl 1/1
5-I-BF [c]	0.28	0.85	15 min	85	15	—	MeI

[a] MeLi was the reagent (see text). [b] Traces. [c] Reactions performed at —100° C.

The above results suggest that the reaction between 2-halobenzothiazoles and the organocopper compounds proceeds through metal—halogen exchange according to eq. 1 and 2.

SCHEME 1

$$\text{2-BT-X} + \text{Me}_2\text{CuLi} \rightleftharpoons \text{(BT)MeCuLi} + \text{MeX} \tag{1}$$

$$\text{(BT)MeCuLi} \left[\begin{array}{l} \xrightarrow{H^+} \text{BT-H} + \text{CH}_4 \\ \xrightarrow{O_2} \text{2-Me-BT} \\ \xrightarrow{\text{MeI}} \text{2-Me-BT} \end{array} \right. \tag{2}$$

The reduction product can be obtained by decomposition of the mixed cuprate formed in step 1. The substitution product may arise from the same mixed cuprate during the oxidative work-up or the MeI treatment.

Scheme 1 agrees with the higher reactivity of 2-iodobenzothiazole compared with the compounds involving other leaving groups. The relatively high acidity of the hydrogen at the 2-position of the benzothiazole [5] indicates a high stability for the corresponding carbanionic species.

The behaviour of 2-fluorobenzothiazole in reaction with Me_2CuLi was unexpected, since fluoro derivatives are known either to react with the organometallic compounds to give the substitution products or not to react at all [6].

Finally, a $S_N\text{Ar}$ substitution is likely for the reaction between 2-fluorobenzothiazole and MeLi.

Reactions of halopyridines (II) with $\textit{Me}_2\textit{CuLi}$

The behaviour of 2- and 3-halopyridines in ether at 0° C was investigated. The 2-fluoro and 2-chloro derivatives were recovered unchanged even after very long reaction times. In contrast, the 2-bromo and 2-iodo derivatives yielded a mixture of 2-methylpyridine and pyridine. The relative amount of the reduction and substitution products was dependent upon the nature of the substrate and the reaction conditions. 3-Iodopyridine was also found to react with Me_2CuLi to give a quantitative yield of the unsubstituted pyridine, but its reactivity appeared to be lower than that of the 2-iodo derivative, and this was confirmed by competitive experiments involving a deficiency of cuprate.

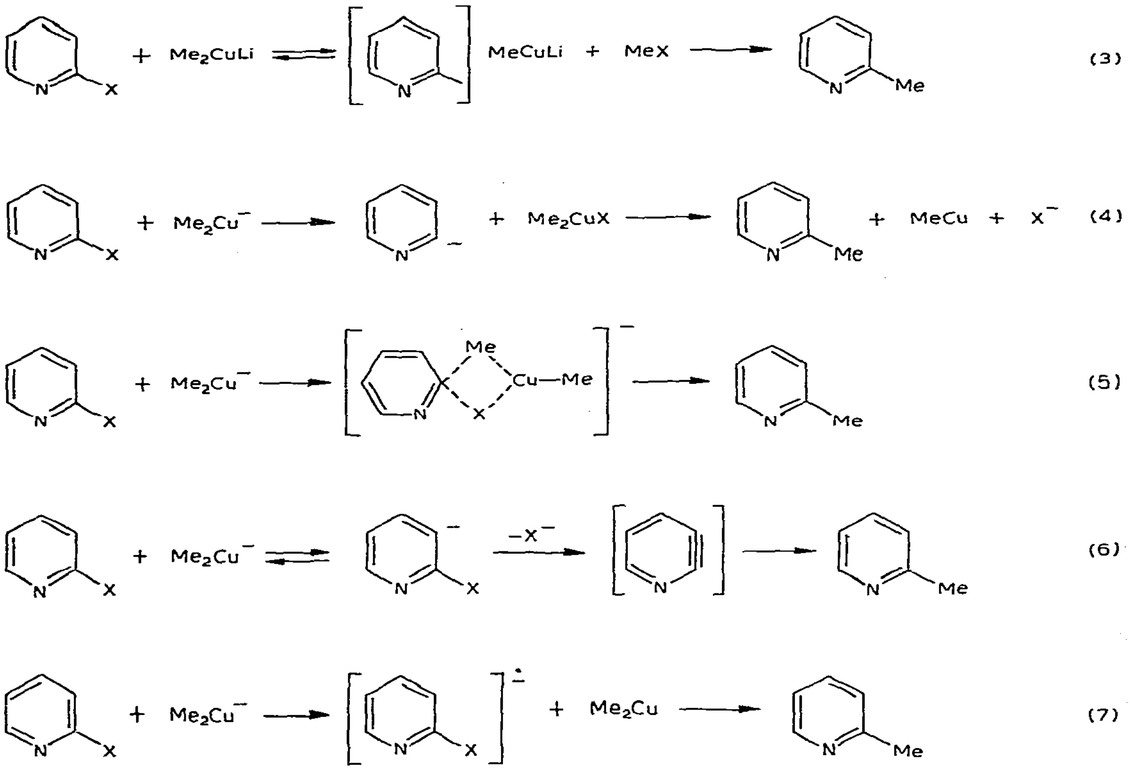
The results obtained with the pyridine system indicate that besides the reduction product (which is probably derived from a dissymmetric cuprate as in the case of the benzothiazole derivatives), the C—C cross-coupling is also formed even without MeI or oxygen treatment. As far as the origin of this process is concerned the higher reactivity of the iodo derivative compared with the other halides does not favour a $S_N\text{Ar}$ mechanism. We are thus left with the other mechanistic possibilities outlined in Scheme 2.

The mixed cuprate could react with the methyl iodide present in the reaction medium or decompose to products (eq. 3).

As a variant of this route, a different carbanionic species could be formed by attack at the halogen, and give rise subsequently to the substitution product (eq. 4).

A concerted substitution could occur. Metal-leaving group interaction of the type shown (eq. 5) may play a role [4,7,8]. As required for this unusual mecha-

SCHEME 2



nism [8,9], we have found that the iodo derivatives are more reactive than the other halides. Furthermore, the higher reactivity of the 2-iodo derivatives compared with the 3-isomer could be attributed to the higher electrophilicity of the position close to the nitrogen.

The elimination—addition mechanism cannot in principle, be ruled out. Indeed, the lack of substitution in position 3 could be explained in terms of the known behaviour of 2,3-didehydropyridine in similar reactions [10]. However, it is known that, because of the low basicity compared with the nucleophilicity of the cuprate reagent, dehydrohalogenation processes are rare [2,11], and are not found even for substrates which undergo elimination very easily [4]. Thus route 6 must be considered unlikely.

Finally, the role of a one-electron transfer process (eq. 7) cannot be clarified here. Indeed, the most appropriate test for this mechanism is based upon stereochemical experiments [1h,4,11], which obviously cannot be performed in our case.

Reactions of the halogenobenzofurazans (III)

The 4-iodo- and 5-iodo-benzofurazans were studied and found to be very reactive toward lithium dimethylcuprate. Reduction and substitution products were formed in both the presence and absence of MeI. The behaviour of this system can thus be interpreted in terms of the proposals above for the benzothiazole and pyridine systems.

Conclusions

This preliminary survey has revealed that a competition between cross-coupling and reductive dehalogenation occurs when heteroaromatic halides react with lithium dimethylcuprate. The relative importance of the two pathways can be varied by changing the leaving group and reagent, as shown by the results with 2-fluorobenzothiazode Several mechanistic possibilities can be envisaged for the substitution, but, the higher reactivity of the iodides reveals that the classical S_NAr addition—elimination process, plays a minor role even when activated heteroaromatic halides are used.

Experimental

NMR and IR spectra were recorded with a Varian HA 100 spectrometer and with a Perkin—Elmer spectrophotometer Mod. 177 respectively.

Materials. Diethyl ether was a good commercial quality product (RS Carlo Erba) and was purified by distillation from sodium wire. Pyridine, 2-fluoro-, 2-chloro-, 2-bromo-, 3-iodo- and 2-methyl-pyridine and benzothiazole were good quality commercial products (Fluka), and were purified by distillation or crystallization. 2-Iodobenzothiazole [12] m.p. 79—80°C, 2-methylbenzothiazole [13] b.p. 223—225°C, 2-iodopyridine [14] b.p. 93°C/13 mmHg, benzofurazan [15] m.p. 52—53°C, 4-methylbenzofurazan [16] m.p. 43—44°C, 5-methylbenzofurazan [16,17] m.p. 36—37°C, 4-iodobenzofurazan [15] m.p. 94.5—95.5°C, and 5-iodobenzofuran [15] m.p. 93.5—94.5°C were prepared by reported procedures.

Lithium dimethyl- and diphenyl-cuprates were obtained from salt-free solutions of methyllithium and phenyllithium which were made from MeI and PhBr respectively.

Reactions. In a typical procedure, to a solution of Me_2CuLi (0.61 mmol) prepared as reported [4], in 10 ml of diethyl ether at 0°C and under an argon stream, 0.1446 g (0.55 mmol) of 2-iodobenzothiazole in 5 ml of diethyl ether were added dropwise with stirring. The solution was quenched after 45 min with HCl 1/1, diluted with water, treated with 10% NH_4OH, and extracted with diethyl ether. The organic extracts were dried over Na_2SO_4 and the solvent removed in vacuo. The products were identified by comparison of their IR and NMR spectra, TLC and GLC retention times with those of authentic samples.

Acknowledgment

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