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REACTION OF 2-HETEROSUBSTITUTED BENZOTHIAZOLES WITH ALLYLIC GRIGNARD REAGENTS

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Abstract - The title benzothiazoles 1 react with allylic Grignard reagents affording 2-allylbenzothiazoles 5, 2,2-diallylbenzothiazolines 6 and N-triallylmethyl-o-aminobenzenethiols as disulphides 7 depending upon the experimental conditions. The reaction is considerably influenced by the solvent used and the nature of the allylic Grignard. A possible mechanism for the formation of compounds 5, 6 and 7 is reported.

The ring opening of the thiazole system has received considerable attention, mainly over the past ten years due to both its inherent mechanistic interest and possible synthetic usefulness. Thus, base-promoted[1] and metal-catalysed[2] ring opening reactions of the thiazole nucleus have been studied, and the application in synthesis of such a ring cleavage has been reported by Corey[3] for the preparation of α,β unsaturated aldehydes and ketones and by Meyers[4] for the synthesis of mono-, di-, and tri-alkyl acetaldehydes. In Corey's work a prerequisite for the successful ring cleavage of the thiazole system is the methylation of the aza group, which makes the C-N double bond much more susceptible to nucleophilic attack, while in Meyers's ring-opening the major feature rests in the preliminary reduction of the C=N link accomplished using aluminum amalgam. No direct ring opening of the thiazole system by using organometallics has ever been reported though a good deal of work has been done in this area.[3,5,6,7]

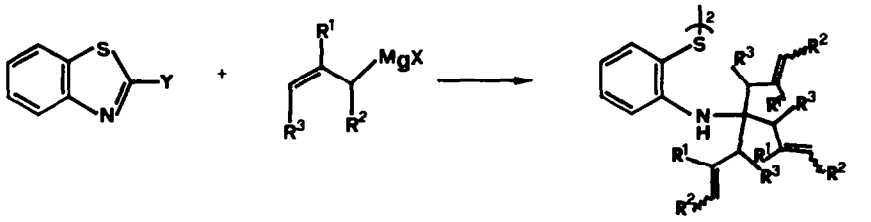
Our researches directed towards ring opening reactions of heterocycles[8,9] by using organometallic reagents have recently led us to discover that benzothiazoles react cleanly with allylic Grignard reagents to give, via a step by step addition of the organometallic reagent, 2,2-allylalkylbenzothiazolines[10] or N-diallylalkyl-o-aminobenzenethiols as disulphides[11] depending upon the experimental conditions. The reaction is specific for allylic Grignards as alkyl or aryl counterparts cause Claisen-type self-condensation with 2-alkylbenzothiazoles[12] and no reaction with 2-halogenobenzothiazoles.[7]

As an extension of the reaction of benzothiazoles with allylic Grignards[7] we

reasoned that the presence of a leaving group in the 2-position of the heterocyclic ring might open, according to the step by step addition process, a way to the synthesis of 2-allylbenzothiazoles, 2,2-diallylbenzothiazolines and N-triallylmethyl-o-aminobenzenethiols. Therefore, we decided to study the reaction of some 2-heterosubstituted benzothiazoles with some allylic Grignard reagents.

RESULTS AND DISCUSSION

The addition of a THF solution of methallylmagnesium chloride 2a (4 mole) to a THF solution of 2-chlorobenzothiazole 1a (1 mole) at room temperature and subsequent quenching of the reaction mixture with aqueous ammonium chloride afforded a high yield of the ring opened product 7a, that was identified by elemental analysis, IR and NMR spectroscopy. Similarly, 2-methoxybenzothiazole 1b and 2-n-propylthiobenzothiazole 1c reacted with 2a providing 7a.



1a: Y= Cl
1b: Y= OMe
1c: Y= SPr^n
1d: Y= I

2a: R^1= Me; R^2= R^3= H
2b: R^1= R^2= H; R^3= Me
2c: R^1= R^2= R^3= H

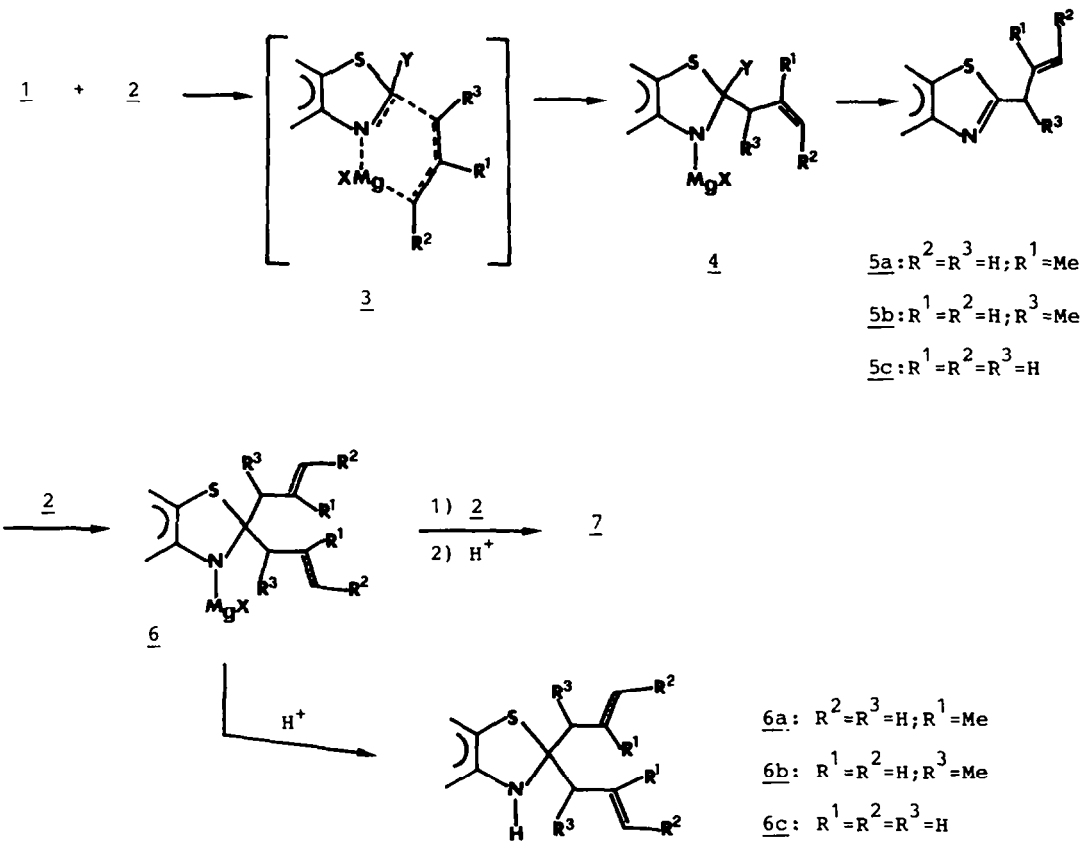
7a: R^1= Me; R^2= R^3= H
7b: R^1= R^2= H; R^3= Me
7c: R^1= R^2= R^3= H

A likely mechanism that may account for the formation of 7a is shown in Scheme I. According to this mechanism, the reaction of 1 (Y= Cl, OMe, SPr^n) with 2a would proceed through the six-membered cyclic transition state 3 to give the benzothiazoline derivative 4, that rapidly undergoes elimination leading to the formation of the 2-(2-methyl-2-propenyl)benzothiazole 5a. The allylic Grignard is specific for the conversion of 1 into 5a, since, as by us reported,[7] 2-chlorobenzothiazole does not react with alkyl or aryl Grignard reagents unless a catalytic amount of a Ni-phosphine complex is present. The specificity of the allylic Grignard may be ascribed to the fact that it may allow a six-membered cyclic transition state such as 3, while the alkyl and the aryl counterparts cannot.

The addition of 2a to the C-N double bond of 5a, as in the case of 2-alkyl- and 2-aryl-benzothiazoles,[11] provides the benzothiazoline derivative 6, that is finally converted into 7a by reaction with the excess 2a.

Since the isolation of 5a and 6a would furnish strong support for the mechanism illustrated in Scheme I, we decided to investigate the reaction between 1 and 2 in more detail, particularly with reference to the solvent, the reactants ratio and steric factors in the organometallic reagent. We found that treatment of 1a or 1b with 2a by using a 1:1 molar ratio leads to a mixture of 5a, 6a and starting material. The most significant results are summarised in the Table. As can be seen, no large variation of the 5a/6a ratio occurs on varying the temperature, while a

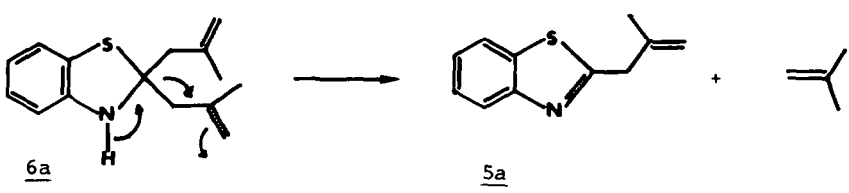
SCHEME I



notable solvent dependence is observed (entries 2-5 and 15-17). Indeed, rather surprisingly, the use of dichloromethane as solvent gives mainly the 2-methallylbenzothiazole 5a and the 2,2-dimethallylbenzothiazoline 6a if a 1:1.2 and 1:2.2 (2.8) molar ratio between reactants is used respectively.

Interestingly, the benzothiazoline 6a, if allowed to stand on silica gel, slowly converts into the 2-methallylbenzothiazole 5a. An ene-type reaction may be involved in such a conversion, as shown in Scheme II, also in view of the fact that benzothiazolines have been reported to convert to benzothiazoles on heating.[13]

SCHEME II



The reaction of 1a or 1b with the crotylmagnesium bromide 2b either in THF or CH_2Cl_2 leads substantially to the formation of 2-(1-methyl-2-propenyl)benzothiazole 5b or 2,2-bis(1-methyl-2-propenyl)benzothiazoline 6b depending upon the reactants molar ratio used (entries 6,7,9,10 and 18-20). It is worth noting that in the reaction of 1a or 1b with 2b only a very low yield of the ring opened product 7b forms even using a large excess of the Grignard reagent. This might likely be ascribed to the steric hindrance exerted by the two allylic groups in the benzothiazoline 6b that makes the approach of the third equivalent of the Grignard reagent, necessary for the formation of 7b, rather difficult. It is also noteworthy that in both the benzothiazole 5b and the benzothiazoline 6b the allylic groups are attached through the more substituted position. This is in agreement with the mechanism postulated for the addition of the allylic Grignard to the C-N double bond of the thiazole system if one considers that there exists an equilibrium between the two species (S_1) and (S_2) of the butenyl Grignard prepared from crotyl bromide, in which the form (S_1), that is that responsible for the formation of the branched chain product, largely predominates.[14] The same results are obtained if the Grignard reagent is prepared starting from 3-chloro-1-butene.

(S_1) (S_2)

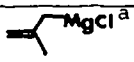
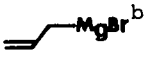
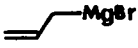
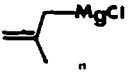
The formation of the benzothiazole 5b can be made exclusive by carrying out the reaction of 1a with 2b in the presence of a catalytic amount (3%) of $NiCl_2$ (dppe) (dppe= $Ph_2PCH_2CH_2PPh_2$) (entry 8).

As can be seen in the Table, it turns out to be rather difficult to control the reaction of 1a or 1b with 2-propenylmagnesium bromide 2c in either THF or CH_2Cl_2 in order to make the 2-allylbenzothiazole 5c and the 2,2-diallylbenzothiazoline 6c form preferentially. Indeed, low conversion of 1a or 1b is observed by using a 1:1 reactants molar ratio, while for higher ratios the ring opened product 7c forms together with 5c and 6c or exclusively (entries 11-13 and 21-23).

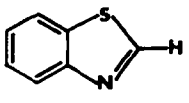
When the 2-iodobenzothiazole 1d (1 mole) is treated with 2a (2.2 mole or more) in THF a mixture of the unsubstituted benzothiazole 8 and the dimethallylmethyl-o-aminobenzenethiol 9 as disulphide was obtained. The outcome of this reaction may likely be accounted for by assuming a nucleophilic attack of the allylic Grignard on the halogen of 1d, followed by the release of the benzothiazole as anion; protonation would then give 8. The ring opened compound 9 would then derive from 8 by reaction with 2a as previously reported.[7]

In conclusion, starting from benzothiazoles having reasonable leaving groups in the 2-position it is possible to prepare 2-allylbenzothiazoles or 2,2-diallylbenzothiazolines or N-triallylmethyl-o- aminobenzenethiols as disulphides under proper experimental conditions. These novel 2,2-diallylbenzothiazolines appear to be potentially useful as precursors of diallyl carbonyls and the N-triallylmethyl-o-aminobenzenethiols may be used for the synthesis of more complex heterocycles.

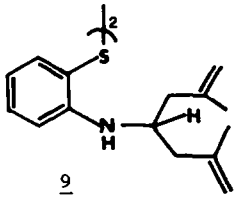
TABLE. Reactions of 2-heterosubstituted benzothiazoles with allylic Grignard reagents.

Entry	Benzo-thiazole	Grignard Reagent	Reactants Molar Ratio	Solvent	Temp. °C	Reaction products % yield[c, f]			
						Starting Material	Cross-Coupling	Benzo-thiazoline	Ring opening
1	1a	 [a]	1:4.4	THF	25	—	—	—	80
2	"	"	1:1.1	"	"	20	49	15	—
3	"	"	"	"	0	26	39	10	—
4	"	"	1:1.2	CH_2Cl_2	"	17	58	18	—
5	"	"	1:2.8	"	"	—	—	86	9
6	"	 [b]	1:1.2	THF	25	—	69	—	—
7	"	"	1:4	"	0	—	—	70	12
8	"	" [d]	1:1.8	"	"	—	85	—	—
9	"	"	1:1.9	CH_2Cl_2	"	—	69	3	—
10	"	"	1:3.3	"	"	—	—	97	—
11	"	 [b]	1:1	"	"	48	42	3	—
12	"	"	1:2.2	"	"	20	33	18	21
13	"	"	1:4	"	"	—	—	—	89
14	1b		1:4.4	THF	25	—	—	—	89
15	"	"	1:1	"	0	10	43	22	5
16	"	"	1:1.2	CH_2Cl_2	"	—	57	25	10
17	"	"	1:2.2	"	"	—	—	88	8
18	"		1:1	THF	"	5	67	13	—
19	"	"	1:1.3	CH_2Cl_2	"	—	77	9	—
20	"	"	1:3.3	"	"	—	—	83	4
21	"		1:1	"	"	28	38	17	10
22	"	"	1:2.2	"	"	19	31	20	23
23	"	"	1:4	"	"	—	—	—	87
24	1c	"	1:4.4	THF	25	—	—	—	81
25	1d		1:4.4[e]	"	"	—	—	—	—
26	"	"	1:2.2[e]	"	"	—	—	—	—

a) Grignard reagent prepared in THF; b) Grignard reagent prepared in ether; c) Yield based on the starting material and determined on isolated, purified products; d) Reaction carried out in the presence of a catalytic amount (3% with respect to the Grignard reagent) of $NiCl_2(dppe)$ (dppe = $Ph_2PCH_2CH_2PPh_2$); e) The reaction leads to a mixture of compound 8 (43%) and compound 9 (25%); f) All new compounds gave satisfactory microanalytical data for C, H, and N.



8



9

Experimental

^{1}H NMR spectra were recorded on a Varian EM 360A or a Varian EM 390 spectrometer and chemical shifts are reported in parts per million (δ) from internal Me_4Si. IR spectra were recorded on a Perkin-Elmer 681 spectrometer. Thin-layer chromatography (TLC) was performed on silica gel sheets with fluorescent indicator (Stratocrom SIF, Carlo Erba). Column chromatography was carried out by using 70-230 mesh silica gel from Merck.

Materials. Tetrahydrofuran (THF) and diethyl ether from commercial sources (RS, Carlo Erba) were purified by distillation (twice) from sodium wire in a N_2 atmosphere. Dichloromethane (RS, Carlo Erba) was purified by distillation. All other chemicals were commercial grade and were purified by distillation or crystallisation prior to use. 2-Methoxy-,[15] 2-n-propylthio-,[16] and 2-iodo-benzothiazole[17] were prepared according to the reported procedures. 2-Propenylmagnesium bromide in ether and 2-methyl-2-propenylmagnesium chloride in THF were prepared by following the procedure reported for 1-methyl-2-propenylmagnesium bromide[18] in ether.

Reaction in THF: General Procedure. To a stirred solution of 1 (6 mmole) in THF (25 ml) was added the appropriate number of mmole (see Table) of the Grignard reagent (0.70 N) under a nitrogen atmosphere. The yellow solution was stirred at the chosen temperature up to the disappearance of the starting material or as long as TLC showed no further change. Then the reaction mixture was quenched with a saturated aqueous ammonium chloride solution (30 ml), extracted with ether (3 x 30 ml), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The reaction products were purified or separated by column chromatography (silica gel; ether/petrol 1:9). IR and NMR data are given below.

Reaction in CH_2Cl_2: General Procedure. To a stirred solution of 1 (6 mmole) in CH_2Cl_2 (60 ml) was added the Grignard reagent (0.7 N) in THF or ether and the procedure carried out as above.

2-(2-methyl-2-propenyl)benzothiazole 5a. oil; IR(neat): 1640 (C=C) cm^{-1}; ^{1}H NMR (CCl_4): δ 2.8(s, 3H), 3.7 (s,2H), 7.0-8.0 (m, 4H).

2-(1-methyl-2-propenyl)benzothiazole 5b. oil; IR(neat): 1655 cm^{-1}; ^{1}H NMR (CCl_4): δ 1.5 (d, 3H), 3.8 (m, 1H), 4.8-5.2 (m, 2H), 5.8-6.3 (m, 1H), 7.0-8.0 (m, 4H).

2-(2-propenyl)benzothiazole 5c. oil; IR(neat): 1640 (C=C) cm^{-1}; ^{1}H NMR (CCl_4): δ 3.8 (m, 2H), 4.9-5.3 (m, 2H), 5.5-6.3 (m, 1H), 7.0-7.9 (m, 4H).

2,2-bis(2-methyl-2-propenyl)benzothiazoline 6a. oil; IR (neat): 3380 (NH) and 1635 (C=C) cm^{-1}; ^{1}H NMR (CCl_4): δ 1.8 (s,6H), 2.5 (s,4H), 4.0 (bs, 1H that exchanges with D_2O), 4.5-4.9 (m, 4H),6.2-6.9 (m,4H).

2,2-bis(1-methyl-2-propenyl)benzothiazoline 6b. oil; IR (neat): 3380 (NH) and 1640 (C=C) cm^{-1}; ^{1}H NMR (CCl_4): δ 1.1 (m,6H), 2.5 (m, 2H), 3.7 (bs, 1H that exchanges with D_2O), 4.8-5.1 (m, 4H), 5.3-6.0 (m, 2H), 6.1-6.9 (m, 4H).

2,2-bis(2-propenyl)benzothiazoline 6c. oil; IR (neat): 3380 (NH) and 1635 (C=C) cm^{-1}; ^{1}H NMR (CCl_4): δ 2.5 (d, 4H), 3.8 (bs, 1H that exchanges with D_2O), 4.8-5.2 (m, 4H), 5.3-6.1 (m, 2H), 6.2-6.9 (m, 4H).

2,2'-dithiodi-[N-(tri-2-methyl-2-propenyl)methyl]aniline 7a. oil; IR (neat): 3380 (NH) and 1640 (C=C) cm^{-1}; ^{1}H NMR (CCl_4): δ 1.8 (s,9H), 2.5 (s, 6H), 3.7 (bs, 1H that exchanges with D_2O), 4.8 (m, 6H), 6.0-7.2 (m, 4H).

2,2'-dithiodi-[N-(tri-1-methyl-2-propenyl)methyl]aniline 7b. oil; IR (neat): 3370 (NH) and 1640 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$):δ0.8-2.0 (cm, 9H), 2.5-3.2 (m, 3H), 4.8-6.6 (cm, 10H, 1NH), 6.7-7.6 (m, 4H).

2,2'-dithiodi-[N-(tri-2-propenyl)methyl]aniline 7c. oil; IR (neat): 3385 (NH) and 1645 (C=C) cm^{-1}; ^{1}H NMR (CCl_4): δ 2.2-2.4 (d, 6H), 3.8 (bs, 1H that exchanges with D_2O), 4.7-5.1 (m, 6H), 5.2-6.0 (m, 3H), 6.2-7.3 (m, 4H).

2,2'-dithiodi-[N-(di-2-methyl-2-propenyl)methyl]aniline 9. oil; IR (neat): 3385 cNH) and 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.8 (s, 6H), 2.2 (d, 4H), 3.7 (m, 1H), 4.9 (s, 4H), 5.1 (bs, 1H that exchanges with D_2O), 6.7-7.3 (m, 4H).

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