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RING OPENING OF BENZOTHIAZOLES WITH ALLYLIC GRIGNARD REAGENTS

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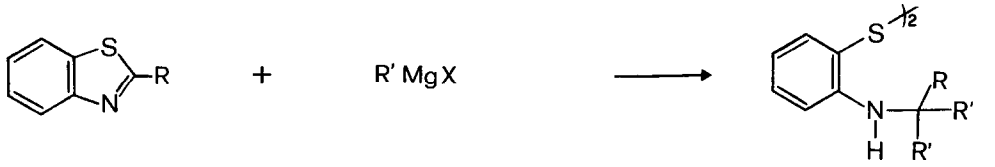
Summary: A novel ring opening reaction of the benzothiazole system with allylic Grignard reagents is reported. A possible mechanism is presented.

The reactions of benzothiazoles with organometallic reagents, planned in order either to better understand the chemistry of the thiazole system, which is active site of the Vitamine B_1, and to synthesize new derivatives, have attracted considerable attention over the past ten years. Thus, cross-coupling with Ni-complex activated Grignard reagents for halogeno-[1] and alkylthio-benzothiazoles[2], metal halogen exchange with cuprates[3] for halogenobenzothiazoles, metallation with organolithium[4] for alkylbenzothiazoles and alkylation in the benzene ring[5] for nitrobenzothiazoles have been reported.

To our knowledge there has not been published any paper dealing with organometallic promoted ring opening reactions of the benzothiazole system. It has only been shown that cleavage of the thiazole ring can be effected under basic conditions for OH^-[6], amines[7] or MeO^-/DMSO[8] and in non basic conditions by metal coordination.[9]

As part of our continuing interest directed to the ring opening reactions of heterocycles by using organometallic reagents,[10] we report here a novel reaction of some benzothiazoles with allylic Grignard reagents.

The addition of 2-methyl-2-propenylmagnesium chloride 2a (2.2 mole) to a THF solution of benzothiazole 1a (1 mole) at room temperature and subsequent quenching with aqueous ammonium chloride afforded very high yield of the ring opened product 3a that was characterised by elemental analysis and IR, NMR and Mass spectroscopy. The conversion of 1a was not complete when a 1:1 molar ratio between 1a and 2a was used. Similarly, the reaction of 1a (1 mole) with 2-propenylmagnesium bromide 2b (2.2 mole) gave compound 3b and benzothiazoles 1b, 1c, 1d, 1e and 1f reacted with 2-methyl-2-propenylmagnesium chloride 2a to furnish compounds 3c, 3d, 3e, 3f and 3g respectively[11] (see Table).



1a R = H
1b R = CH_3
1c R = C_2H_5
1d R = Ph
1e R = CH_2Ph
1f R = $CH_2CH_2CH_3$

2a R' = CH_2-C(CH_3)=CH_2, X = Cl
2b R' = CH_2-CH=CH_2, X = Br

3a R = H, R' = CH_2-C(CH_3)=CH_2
3b R = H, R' = CH_2-CH=CH_2
3c R = CH_3, R' = CH_2-C(CH_3)=CH_2
3d R = C_2H_5, R' = "
3e R = Ph, R' = "
3f R = CH_2Ph, R' = "
3g R = $CH_2CH_2CH_3$, R' = "

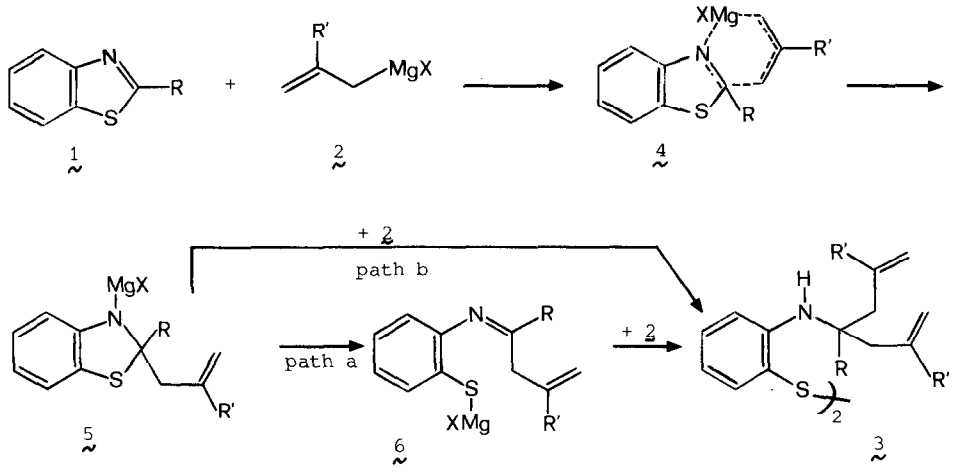
Table. Ring opened products 3a-g from reaction of benzothiazoles 1a-f with allylic Grignard reagents at room temperature.

Benzothiazole	Grignard Reagent	Solvent	Product (yield %)[a]
1a	2a	THF	3a (89)
1a	2b[b]	ether	3b[c] (73)
1a	2b	ether	3b (90)
1b	2a	THF	3c (86)
1c	2a	THF	3d (47)
1d	2a	THF	3e (83)
1e	2a	THF	3f (92)
1f	2a	THF	3g (88)

[a]Yield determined on isolated purified products. [b]Reaction carried out at -50°C and quenched with sat NH_4Cl after 1h. [c]Yield based on converted starting material.

The present ring opening reaction of benzothiazoles 1 seems to be specific of allylic Grignard reagents as no reaction took place when 1a was treated with n-BuMgBr and an intractable mixture of many products characterised the reaction of 1a with PhMgBr and $PhCH_2MgBr$. The peculiar behaviour exhibited by the allylic Grignard may tentatively be ascribed to the fact that such reagents may interact with the thiazole system, via a preliminary coordination of magnesium on the aza group, to give a six-membered cyclic transition state of the kind 4, as shown

in the scheme . According to this scheme, a benzothiazoline 5 would form as an intermediate and the final ring opened product 3[14] might derive from 5 either directly by reaction with the Grignard reagent 2 (path b) or via the Schiff's base 6 (path a). However, attempted trapping of the postulated intermediate 5 by carrying out a reaction of 1a with 2b at -50° C and using a 1:1 reactants molar ratio failed. Only in the case of 2-ethylbenzothiazole 1c we have been able to trap the benzothiazoline intermediate 7[12] (35%), derived from 5 (R = C_2H_5, R'= CH_3).



1 2 4 5 6 3

Work is in progress to get more insights of the mechanism which is operating in the ring opening reaction of benzothiazoles described here. However, whatever the mechanism, we wish to stress that the reaction is quite useful from the synthetic viewpoint as it opens an easy, convenient and high yield way to 2-monoalkylaminothiophenols[13] (as disulfides) which are to be considered very important building blocks for the construction of N-alkyl nitrogen and sulfur containing heterocyclic systems.

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11) Typical experimental conditions were those described for the reaction of 1a with 2a.To a solution of 1a (3.7 mmol) in 10 ml of dry THF was added a solution of 2a (8.1 mmol) in THF dropwise and with stirring at room temperature under nitrogen. Stirring was continued of 1h and then the red mixture was quenched with aqueous sat NH_4Cl. Extraction with ether, drying over $MgSO_4$ and removal of the solvent under reduced pressure gave the ring opened product that was purified by crystallisation or by column chromatography. New compounds had the following data. 3a, m.p. 59-61°C (ether/petrol). IR (CH_2Cl_2): 3400 and 1650 cm^{-1}. ^{1}HNMR ($CDCl_3$, D_2O): δ 1.73(s, 6H), 2.2(d, 4H, J 7.5Hz), 3.65(m, 1H, J 7.5Hz), 4.8(s, 4H), 6.3-7.3(m, 4H). $M^+/_2$= 246. 3b, oil. IR (neat): 3400 and 1650 cm^{-1}. ^{1}HNMR ($CDCl_3$, D_2O): δ 2.2(t, 4H), 3.5(m, 1H), 4.9(bs, 2H), 5.1(bs, 2H), 5.4-6.1(m, 2H), 6.3-7.4(m, 4H). 3c, m.p. 102-104°C (ethanol). IR (CH_2Cl_2): 3400, 1650 cm^{-1}. ^{1}HNMR ($CDCl_3$): δ 1.35(s, 3H), 1.75(s, 6H), 2.5(dd, 4H, AB system), 4.68(bs, 2H), 4.8(bs, 2H), 5.2(bs, 1H), 6.1-7.2(m, 4H). 3d, thick oil. IR (neat): 3410 and 1665 cm^{-1}. ^{1}HNMR ($CDCl_3$, D_2O): δ 0.95(t, 3H), 1.75(s, 6H), 1.82 (q, 2H), 2.5(dd, 4H, AB system), 4.75(s, 2H), 4.9(s, 2H), 6.5-7.4(m, 4H). 3e, m.p. 46-48°C (ether/petrol). IR (CH_2Cl_2): 3410 and 1655 cm^{-1}. ^{1}HNMR ($CDCl_3$, D_2O): δ 1.43(s, 6H), 2.9(s, 4H), 4.75(s, 2H), 4.94(s, 2H), 6.15-7.5(m, 9H). 3f, oil. IR(neat):3380 and 1640 cm^{-1}. ^{1}HNMR ($CDCl_3$,D_2O): δ 1.8(s,6H),2.5(bs,4H),3.15(s,2H),4.9(bs,4H),6.3-7.5(m,9H). 3g, oil. IR(neat): 3395 and 1645 cm^{-1}. ^{1}HNMR($CDCl_3$,D_2O): δ 0.9(t,3H),1.75(m,10H),2.5(dd,4H,AB system),4.7(bs, 2H),4.85(bs,2H),6.3-7.4(m,4H).

12) Benzothiazoline 7 shows: oil. IR(neat):3395 and 1655 cm^{-1}. ^{1}HNMR($CDCl_3$): δ 1.05(t,3H),1.9 (s,3H),1.95(q,2H),2.7(dd,2H,AB system),4.2(bs,1H, exchange with D_2O),4.8(s,1H),5.0(s,1H), 6.6-7.1(m,4H).

13) The only known procedure to 2-monoisoalkylaminothiophenols is the lithium aluminum hydride reductive ring opening of benzothiazolines. W.Mueller,Eur.Pat.Appl.,26,469(1981); C.A. 95,132570n(1981).

14) Disulfides 3 could actually originate during the workup following upon an easy oxidation of the corresponding thiols initially formed.

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