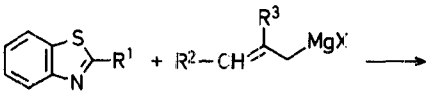
Reaction of Benzothiazoles with Allylic Grignard Reagents: Synthesis of 2-Allylbenzothiazolines

Francesco BABUDRI, Saverio FLORIO*, Giuseppe INGUSCIO

Dipartimento di Chimica, Università, Via Amendola 173, I-70126 Bari, Italy

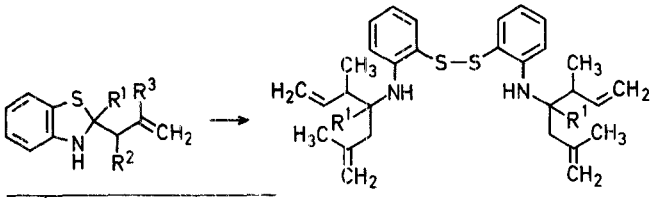
We have recently found that benzothiazoles (**1**) undergo ring opening upon treatment with allylic Grignard reagents (**2**) to give *N*-(1,1-diallylalkyl)-2-aminobenzenethiols which are isolated as the disulphides[1]. The reaction was found to be specific for allylic Grignard reagents. Alkyl- and arylmagnesium halides did not react under the same conditions or promoted Claisen-type self-condensation under more severe conditions[2]. Ring cleavage was thought to proceed through a cyclic transition state and benzothiazolines **3** were supposed to be intermediates; attempted trapping failed, however. In search for evidence supporting the proposed mechanism and considering that 2-allylbenzothiazolines also are potential precursors of allyl ketones and that they might be prepared in this way, we decided to investigate the reaction of **1** with **2** in more detail, particularly with reference to solvent, temperature, and ratio of reactants.

At various temperatures and in solvents such as tetrahydrofuran, ether, and dimethoxyethane, the ring-cleavage products **4** are formed almost exclusively in all cases even when a 1 : 1 molar ratio of reactants is used. Therefore, we were quite surprised to find that benzothiazolines **3** could be obtained in high yields when the reactions were carried out in dichloromethane. Thus, treatment of **1a** with equimolecular amounts of **2a** or **2b** in dichloromethane furnishes high yields of **3aa** and **3ab**, respectively. Similarly, benzothiazoles **1b, c, d** react with **2a, b** to give almost pure benzothiazolines **3**, the only contaminations being some unreacted starting material and small amounts of the ring-cleavage products.



1a $R^1 = CH_3$
1b $R^1 = C_2H_5$
1c $R^1 = -CH_2-C_6H_5$
1d $R^1 = n\text{-}C_3H_7$

2a $R^2 = CH_3$; $R^3 = H$
2b $R^2 = H$; $R^3 = CH_3$

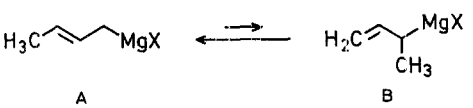


3	R^1	R^2	R^3
aa	CH_3	CH_3	H
ba	C_2H_5	CH_3	H
ca	$-CH_2-C_6H_5$	CH_3	H
da	$n\text{-}C_3H_7$	CH_3	H
ab	CH_3	H	CH_3
bb	C_2H_5	H	CH_3
cb	$-CH_2-C_6H_5$	H	CH_3
db	$n\text{-}C_3H_7$	H	CH_3

4a $R^1 = CH_3$
4b $R^1 = C_2H_5$
4c $R^1 = n\text{-}C_3H_7$

The same benzothiazolines **3a–d** in which the allyl group is attached to the more substituted position, are exclusively formed in the reaction of benzothiazoles **1a–d** with the allylic Grignard reagent prepared from 1-bromo-2-butene or 3-chloro-1-butene.

This result may be rationalized in terms of an equilibrium between the two species A and B in which the form A, responsible for the formation of the branched-chain product according to the proposed mechanism[3], largely predominantes[4].



A B

It is worthy of note that the benzothiazolines **3ba**, **3da**, and **3ab** were recovered substantially unchanged upon treatment with butyl- or phenylmagnesium bromide (2 molecular equivalents) even when tetrahydrofuran was used as solvent but that they react smoothly with the allylic Grignard reagent **2a** or **2b** in tetrahydrofuran or ether to give good yields of the ring-cleavage products **4b**, **4c**, and **4a**, respectively.

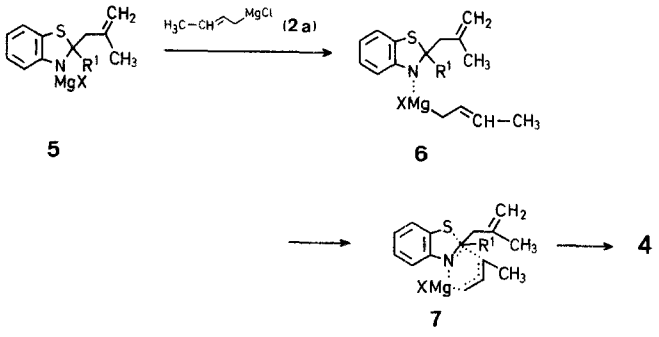
The present reaction of benzothiazoles **1** with Grignard reagents **2** deserves some comments in that it is performed in dichloromethane[5], a solvent quite unusual for Grignard reagents, and leads to

Table. 2-Alkyl-2-allyl-2,3-dihydro-1,3-benzothiazoles (**3**) prepared

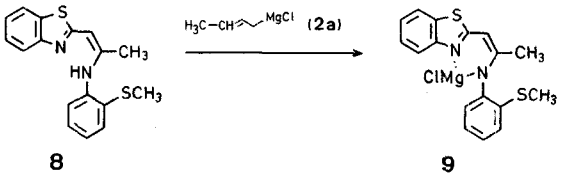
3	Yield[a] [%]	Physical Data [°C]	Molecular Formula[b]	I.R. (neat) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4/TMS_{int}) δ [ppm]
aa	95	oil[c]	$C_{24}H_{30}N_2S_2$ (410.5)	3360 (NH); 1640 (C=C)	1.05 (d, 3H); 1.5 (s, 3H); 2.3–2.8 (m, 1H); 3.8 (br. s, 1H, exchange with D_2O); 4.8–5.2 (m, 2H); 5.3–6.0 (m, 1H); 6.2–6.9 (m, 4H)
ba	98	oil[c]	$C_{26}H_{34}N_2S_2$ (438.6)	3400 (NH); 1650 (C=C)	0.8–1.4 (m, 6H); 1.5–2.0 (m, 2H); 2.4–2.8 (m, 1H); 3.9 (br. s, 1H, exchange with D_2O); 4.7–5.2 (m, 2H); 5.3–6.2 (m, 1H); 6.3–6.9 (m, 4H)
ca	84	m.p. 64–65° (ether)	$C_{36}H_{38}N_2S_2$ (562.7)	3400 (NH); 1640 (C=C)[d]	1.1–1.4 (m, 3H); 2.3–2.7 (m, 1H); 3.2 (m, 2H); 3.9 (br. s, 1H, exchange with D_2O); 4.6–5.3 (m, 2H); 5.5–6.2 (m, 1H); 6.2–7.0 (m, 4H); 7.1 (s, 5H)
da	97	oil[c]	$C_{28}H_{38}N_2S_2$ (466.6)	3380 (NH); 1640 (C=C)	0.8–1.9 (m, 7H); 1.1 (d, 3H); 2.2–2.8 (m, 1H); 3.8 (br. s, 1H, exchange with D_2O); 4.8–5.2 (m, 2H); 5.4–6.0 (m, 1H); 6.2–6.9 (m, 4H)
ab	74	oil[c]	$C_{24}H_{30}N_2S_2$ (410.5)	3360 (NH); 1645 (C=C)	1.6 (s, 3H); 1.8 (s, 3H); 2.5 (dd, 2H); 3.8 (br. s, 1H, exchange with D_2O); 4.6–4.9 (m, 2H); 6.2–6.9 (m, 4H)
bb	79	oil[c]	$C_{26}H_{34}N_2S_2$ (438.6)	3360 (NH); 1645 (C=C)	0.8–2.0 (m, 8H); 1.5 (dd, 2H); 3.8 (br. s, 1H, exchange with D_2O); 4.4–4.9 (m, 2H); 6.2–6.9 (m, 4H)
cb	80	oil[c]	$C_{36}H_{38}N_2S_2$ (562.7)	3380 (NH); 1645 (C=C)	2.8 (s, 3H); 2.5 (s, 2H); 3.1 (dd, 2H); 3.8 (br. s, 1H, exchange with D_2O); 4.8 (m, 2H); 6.3–6.9 (m, 4H); 7.1 (s, 5H)
db	68	oil[c]	$C_{28}H_{38}N_2S_2$ (466.6)	3360 (NH); 1645 (C=C)	0.6–2.0 (m, 10H); 2.6 (dd, 2H); 3.9 (br. s, 1H, exchange with D_2O); 4.6–4.9 (m, 2H); 6.2–6.9 (m, 4H)

[a] Yield of isolated and purified product.
[b] Satisfactory microanalyses obtained: C ±0.30; H ±0.25; N ±0.30.
[c] Isolated and purified by column chromatography.
[d] In CH_2Cl_2 solution.

benzothiazolines **3** whereas the reaction of **1** with **2** in tetrahydrofuran or ether affords the ring-cleavage products **4**. The reaction path in dichloromethane may be rationalized by postulating the existence of the intermediate *N*-(halomagnesio) derivative **5** as an intimate ion pair in which $MgX^{\oplus}$ cannot be replaced by the allylic Grignard reagent to give an intermediate of the type **6** which could then be converted into the ring-cleavage product **4** via a transition state **7**. This assumption is supported by the fact that benzothiazolines **3** react with Grignard reagents **2** in tetrahydrofuran (in which case the exchange reaction **5** → **6** can take place) but do not react with butyl- or phenylmagnesium bromide (2 molecular equivalents). This confirms the particular behaviour of the allylic Grignard reagents.



In this context it should be mentioned that benzothiazole derivative **8** (prepared from 2-methylbenzothiazole by reaction with phenylmagnesium bromide[2]) does not undergo addition of the Grignard reagent to the ring C=N double bond when subjected to the reaction with reagent **2a**, presumably due to abstraction of the N—H proton in **8** with formation of the halomagnesio derivative **9** which is strongly stabilized by chelation involving the heterocyclic ring and therefore reluctant to ring cleavage.



In summary, 2-alkylbenzothiazoles can be easily converted into 2-alkyl-2-allylbenzothiazolines, which are potential precursors of allyl ketones[6], by reaction with allylmagnesium halides in dichloromethane. Further, these benzothiazolines may be converted into bis[2-(1,1-diallylalkylamino)-phenyl] disulfides having two different allyl groups.

The ^{1}H-N.M.R. spectra of compounds **4** were recorded with a Varian XL 200 instrument, those of compounds **3** with a Varian EM 360 instrument.

2-Methyl-2-(1-methylallyl)-2,3-dihydro-1,3-benzothiazole (3aa); Typical Procedure:

To a stirred solution of 2-methylbenzothiazole (**1a**; 1 g, 6.7 mmol) in dichloromethane (50 ml) at 0 °C is added a 0.72 normal ethereal solution of 1-methylallylmagnesium chloride (**2a**; 10.7 ml, 6.7 mmol). Stirring is continued for 15 min and the reaction then quenched by adding saturated ammonium chloride solution (20 ml) to the yellow mixture. The dichloromethane phase is separated and dried with sodium sulfate. The solvent is removed under reduced pressure and the product **3aa** purified by column chromatography on silica gel using ether/petroleum ether (1/4) as eluent.

Bis[2-(1-methallyl-1,2-dimethyl-3-butenylamino)-phenyl] Disulfide (4a); Typical Procedure:

A 0.74 normal ethereal solution of 1-methylallylmagnesium chloride (**2a**; 9.6 ml, 7.08 mmol) is added dropwise to a stirred solution of 2-

methallyl-2-methyl-2,3-dihydro-1,3-benzothiazole (**3ab**; 0.66 g, 3.22 mmol) in ether (15 ml) at 0 °C. Stirring is continued for 10 min and the reaction then quenched by adding saturated ammonium chloride solution (20 ml) to the yellow mixture. The resultant mixture is extracted with ether (3 × 25 ml). The organic extract is dried with sodium sulfate and evaporated to give the nearly pure product **4a** which is further purified by column chromatography on silica gel using ether/petroleum ether (1/4) as eluent.

Disulfide **4a**; yield: 74%; oil.

$C_{32}H_{44}N_2S_2$	calc.	C 73.8	H 8.5	N 5.4
(520.7)	found	73.6	8.3	5.4

I.R. (neat): ν = 3380 (NH); 1640 (C=C) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 1.05 (m, 3H); 1.4 (s, 3H); 1.8 (s, 3H); 2.5 (m, 2H); 2.9 (m, 1H); 4.6–5.4 (m, 5H, 1NH exchangeable with D_2O); 5.9 (m, 1H); 6.3–7.5 ppm (m, 4H).

Disulfide **4b**; yield: 71%; oil.

$C_{34}H_{48}N_2S_2$	calc.	C 74.5	H 8.8	N 5.1
(548.8)	found	74.5	8.8	5.2

I.R. (neat): ν = 3380 (NH); 1640 (C=C) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 0.9 (m, 3H); 1.1 (m, 3H); 1.7–2.0 (m, 5H); 2.3–2.6 (m, 2H); 2.85 (m, 1H); 4.7–5.1 (m, 5H, 1NH, exchangeable with D_2O); 6.0 (m, 1H); 6.3–7.5 ppm (m, 4H).

Disulfide **4c**; yield: 73%; oil.

$C_{36}H_{52}N_2S_2$	calc.	C 75.0	H 9.0	N 4.9
(576.8)	found	75.1	9.2	4.7

I.R. (neat): ν = 3385 (NH); 1645 (C=C) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 0.88 (m, 3H); 1.06 (m, 3H); 1.4 (m, 2H); 1.85 (m, 5H); 2.3–2.6 (m, 2H); 2.85 (m, 1H); 4.7–5.35 (m, 5H, 1NH, exchangeable with D_2O); 6.0 (m, 1H); 6.3–7.6 ppm (m, 4H).

We thank CNR and Ministero Pubblica Istruzione (Roma) for financial support.

Received: July 16, 1984

* Address for correspondence.

[1] Babudri, F., Bartoli, G., Ciminale, F., Florio, S., Ingrosso, G. *Tetrahedron Lett.* **1984**, *25*, 2047.

[2] Babudri, F., Ciminale, F., Florio, S. *Tetrahedron Lett.* **1984**, *25*, 2051.

[3] Hill, E.A. *J. Organomet. Chem.* **1975**, *91*, 123.
Cariddu, S., Marongiu, E., Melis, S., Sotgiu, F. *J. Organomet. Chem.* **1976**, *116*, 275.

[4] cf. Nützel, K. in: Houben-Weyl, *Methoden der Organischen Chemie*, 4th Edn., Müller, E., Ed., Vol. 13/2a, Georg Thieme Verlag, Stuttgart, 1973, p. 491.

[5] Viehe, H.G., Reinstein, M. *Chem. Ber.* **1962**, *95*, 2557.

[6] Meyers, A.I., Durandetta, J.L. *J. Org. Chem.* **1975**, *40*, 2021.