Reaction of Benzoxa(thia)zoles with Allenylmagnesium Bromide: Synthesis of Propargylbenzothiazolines and Dipropargylalkyl-*o*-aminophenols

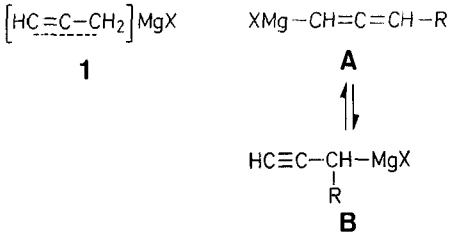
F. Babudri, S. Florio*

Centro di Studio sulle Metodologie Innovative di Sintesi Organiche del C.N.R., c/o Dipartimento di Chimica, Università, Via Amendola 173, 70126 Bari, Italy.

Benzoxazoles **2a–e** and benzothiazole **4a** react with the Grignard reagent prepared from propargyl bromide to give the *N*-dipropargylalkyl-*o*-aminophenols **3a–e** and the *N*-dipropargylalkyl-*o*-aminothiophenol as disulfide **6** respectively. The reaction of benzothiazoles **4b–e** with **1** gives the propargylbenzothiazolines **5b–e** and that of 2-methoxybenzothiazole **8** produces the 2-allenylbenzothiazole **9**.

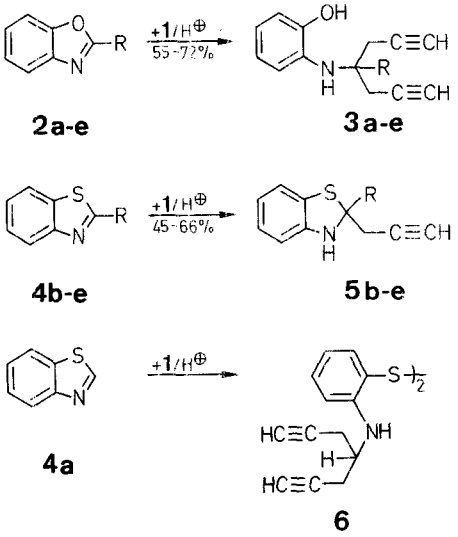
We have recently reported that allylic Grignard reagents, contrary to the alkyl and aryl counterparts, add promptly and directly to the C=N bond of benzoxa(thia)zoles[1]. The reactions were supposed to proceed *via* a S_Ei' mechanism, that is plausible for ambident organometallic reagents[2].

As part of our continuing interest in the reactivity of heterocycles with organometallic reagents we report here on the reaction of benzothiazoles and benzoxazoles with the allenyl(propargyl) Grignard reagent **1**, which, in view of its ambident nature, was expected to behave as the abovementioned allylic Grignards.



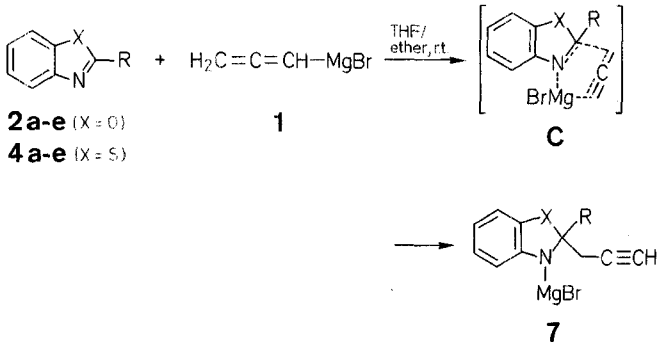
The addition of a three-fold excess of the freshly prepared[3] Grignard reagent **1** to benzoxazoles **2a–e** afforded the dipropargylalkyl-*o*-aminophenols **3a–e** in good yield (Table). The expected propargylbenzoxazolines could not be obtained even using a 1:1 molar ratio between reactants. Also the benzothiazole **4a** underwent ring opening reaction upon treatment with **1** to give 2,2'-dithio-*N*-dipropargylmethyldianiline (**6**) in good yield. Most noteworthy is the formation of the propargylbenzothiazolines **5b–d** in satisfactory yields from benzothiazoles **4b–e** with either a stoichiometric amount or a 3-fold excess of **1**.

If one considers that the ambident Grignard reagent **1** exists[4] as a rapidly equilibrating mixture of the allenic and propargylic forms **A** and **B** and that the allenic form largely predominates, the formation of either the ring opened products **3** and the propargylbenzothiazolines **5** could be explained in terms of a S_Ei'-like mechanism involving the chelate transition state **C** as depicted in Scheme **A**. A deviation of the C=C=C

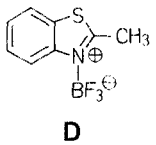


2–5	R
a	H
b	CH_3
c	C_2H_5
d	n-C_3H_7
e	C_6H_5–CH

grouping of the allenic moiety from the linearity may be invoked[5]. The intermediate benzoxa(thia)zoline **7** would give **5** on hydrolysis or the ring opened products **3** upon further reaction with **1**. Accordingly, no reaction occurred when the Grignard reagent **1** was added to the benzothiazole **4b** pretreated with boron trifluoride etherate. Indeed, the existence of **4b** in the complexed form **D** would not allow, according to the S_Ei' mechanism, the cyclic transition state **C**, that involves coordination of magnesium of the Grignard reagent **1** with the unshared electron pair of the aza group.



Scheme **A**



It is remarkable that the propargylbenzothiazolines **5** resist the Grignard reagent present in the reaction medium (even in large excess). As an explanation, one may assume that the second attack of the Grignard reagent on the propargylbenzothiazolinemagnesium bromide **7** (X=S) to cause ring cleavage of the heterocyclic moiety is disfavored for steric reasons when R ≠ H.

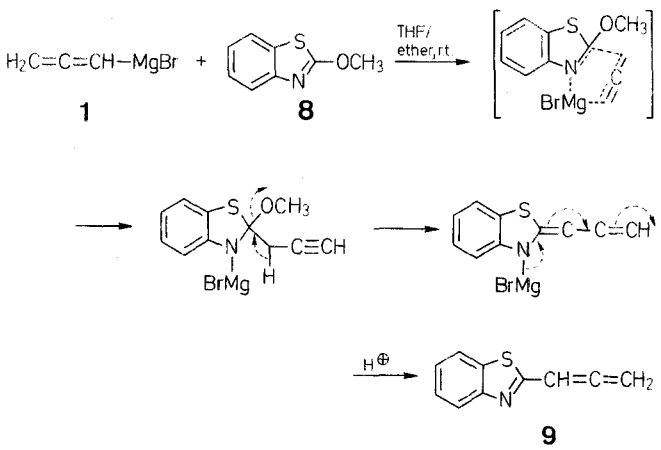
Table. Dipropargylalkyl-*o*-aminophenols **3a–e** and Propargylalkylbenzothiazolines **5b–e** prepared

Compound	Yield[a] [%]	m.p. [°C] (solvent)	Molecular[b] Formula	I.R. (CCl_4) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4/TMS) δ [ppm]
3a	72	oil[c]	$C_{13}H_{13}NO$ (199.2)	3615, 3420, 3315, 2120	1.9 (m, 2H); 2.45 (m, 4H); 3.35 (t, 1H, J = 5 Hz); 4.8 (br.s, 2H, exchangeable with D_2O); 6.3–7.8 (m, 4H)
3b	55	74–75° (ether)	$C_{14}H_{15}NO$ (213.3)	3380, 3320, 2120	1.2 (s, 3H); 2.0 (m, 2H); 2.4 (m, 4H); 6.3–7.3 (m, 4H)[d]
3c	64	39–40° (ether)	$C_{15}H_{17}NO$ (227.3)	3620, 3380, 3320, 2130	0.9 (t, 3H, J = 7 Hz); 1.2–1.8 (m, 2H); 2.0 (m, 2H); 2.8 (m, 4H); 6.3–7.2 (m, 4H)[d]
3d	70	74–75° (ethanol)	$C_{16}H_{19}NO$ (241.3)	3620, 3380, 3320, 2130	0.7–1.8 (m, 7H); 2.0 (m, 2H); 2.35 (m, 4H); 4.9 (br.s, 2H, exchangeable with D_2O); 6.4–7.3 (m, 4H)
3e	55	103–105° (ethanol)	$C_{20}H_{19}NO$ (289.4)	3390, 3330, 2130	2.0 (m, 2H); 2.15 (m, 4H); 2.85 (s, 2H); 6.3–7.3 (m, 9H)[d]
5b	60	oil[c]	$C_{11}H_{11}NS$ (189.3)	3310, 2120	1.75 (s, 3H); 1.9 (m, 1H); 2.2–3.2 (m, 2H); 4.2 (br.s, 1H, exchangeable with D_2O); 6.3–7.1 (m, 4H)
5c	45	oil[c]	$C_{12}H_{13}NS$ (203.3)	3315, 2120	1.0 (t, 3H, J = 7 Hz); 1.8–2.2 (m, 2H); 1.9 (m, 1H); 2.3–3.2 (m, 2H); 4.2 (br.s, 1H, exchangeable with D_2O); 6.3–7.1 (m, 4H)
5d	64	oil[c]	$C_{13}H_{15}NS$ (217.3)	3310, 2120	1.1–2.1 (m, 7H); 1.9 (m, 1H); 2.2–3.2 (m, 2H); 4.2 (br.s, 1H, exchangeable with D_2O); 6.3–7.2 (m, 4H)
5e	66	74–75° (ether)	$C_{17}H_{15}NS$ (265.3)	3310, 2130	2.2 (m, 1H); 2.7 (m, 2H); 3.4 (s, 2H); 4.2 (br.s, 1H, exchangeable with D_2O); 6.3–7.1 (m, 4H); 7.3 (m, 5H)

[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] Spectra after exchange of OH proton with D_2O.

The 2-methoxybenzothiazole **8** has been found to react with **1** producing a reasonable yield of the 2-allenylbenzothiazole **9**, the formation of which might yet be rationalized in terms of a S_Ei' mechanism, involving the attack of the allenic form of the Grignard reagent followed by the elimination of methanol and isomerisation, as shown in scheme **B**.

In summary, benzoxazoles **2** can be easily converted to dipropargylalkyl-*o*-aminophenols **3**, which can be used for the synthesis of tricyclic dienes[6] and phenols fused with 5-membered rings[7], by reaction with allenylmagnesium bromide. Moreover, the reaction of benzothiazoles **4** with the Grignard reagent **1** allows the synthesis of novel and potentially useful propargylbenzothiazolines **5** and the allenylbenzothiazole **9**.



Scheme **B**

Dipropargylmethyl-*o*-aminophenol (3a); Typical Procedure:
To a stirred solution of **2a** (1 g, 8.4 mmol) in dry tetrahydrofuran (15 ml) is added a freshly prepared[3] 1.03 normal solution of allenylmagnesium bromide in ether (24 ml, 25.2 mmol) under nitrogen at room temperature. Stirring is continued for 1.5 h and then the brown mixture is quenched with saturated aqueous ammonium chloride (10 ml). The product formed is extracted with ether (3 × 20 ml), the ether layer is dried with sodium sulfate and the solvent is removed under reduced pressure. Purification is effected by column chromatography on silica gel using ether/petroleum ether (1/4) as eluent resulting in an oil; yield: 1.21 g (72%).

2,2'-Dithio-*N*-dipropargylmethyldianiline (6):
This compound is obtained as an oil starting from **4a** by following the above procedure for the preparation of **3a**; yield: 1.14 g (72%).

$C_{26}H_{22}N_2S_2$ (426.6) calc. C 73.2 H 5.2 N 3.3; found 73.2 5.3 3.4

I.R. (CCl_4): ν = 3310, 2120 cm^{-1}.

^{1}H-N.M.R. (CCl_4): δ = 1.9 (m, 2H); 2.7 (m, 4H); 3.7 (m, 1H); 4.9 (br. s, 1H, exchangeable with D_2O); 6.3–6.7 (m, 2H); 6.8–7.6 ppm (m, 2H).

2-Methyl-2-propargylbenzothiazoline (5b); Typical Procedure:
To a stirred solution of **4b** (1.22 g, 8.2 mmol) in dry tetrahydrofuran (15 ml) is added a freshly prepared[3] 1.03 normal solution of allenylmagnesium bromide in ether (12 ml, 12.6 mmol) under nitrogen at room temperature. After 2 h the resulting brown mixture is quenched with aqueous saturated ammonium chloride and extracted with ether (3 × 15 ml). The ether layer is dried with sodium sulfate, concentrated under reduced pressure and the oily product is purified by column chromatography on silica gel using ether/petroleum ether (1/4) as eluent; yield: 0.92 g (60%).

2-Allenylbenzothiazole (9):
To a stirred solution of **8** (0.5 g, 3.02 mmol) in dry tetrahydrofuran (20 ml) is added a freshly prepared[3] 0.93 normal solution of allenylmagnesium bromide in ether (13 ml, 12.08 mmol) under

nitrogen at room temperature. After 30 min T.L.C. (eluent: ether/petroleum ether (1/4) showed the complete disappearance of the starting benzothiazole **8**. The mixture is quenched with aqueous saturated ammonium chloride, extracted with ether (3 × 15 ml) and the ether layer is dried with sodium sulfate. The crude product obtained after removal of the solvent under reduced pressure is purified by preparative T.L.C. on silica gel plates using ether/petroleum ether (1/4) as eluent to give **9** as an oil; yield: 0.17 g (32%).

$C_{10}H_7NS$	calc.	C 69.4	H 4.0	N 8.1
(173.2)	found	69.5	4.1	8.3

I.R. (CCl_4): ν = 1970, 1941 cm^{-1}.

^{1}H-N.M.R. (CCl_4): δ = 5.25 (d, 2H, J = 7 Hz); 6.6 (t, 1H, J = 7 Hz); 7.2–8.0 ppm (m, 4H).

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