Tetrahedron Letters,Vol.25,No.19,pp 2051-2054,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

SELF-CONDENSATION REACTION OF ALKYLBENZOTHIAZOLES WITH GRIGNARD REAGENTS

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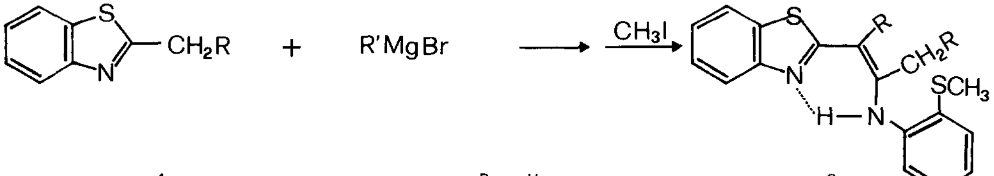
Summary: 2-alkylbenzothiazoles undergo Claisen-type self-condensation reaction simply on treatment with Grignard reagents.

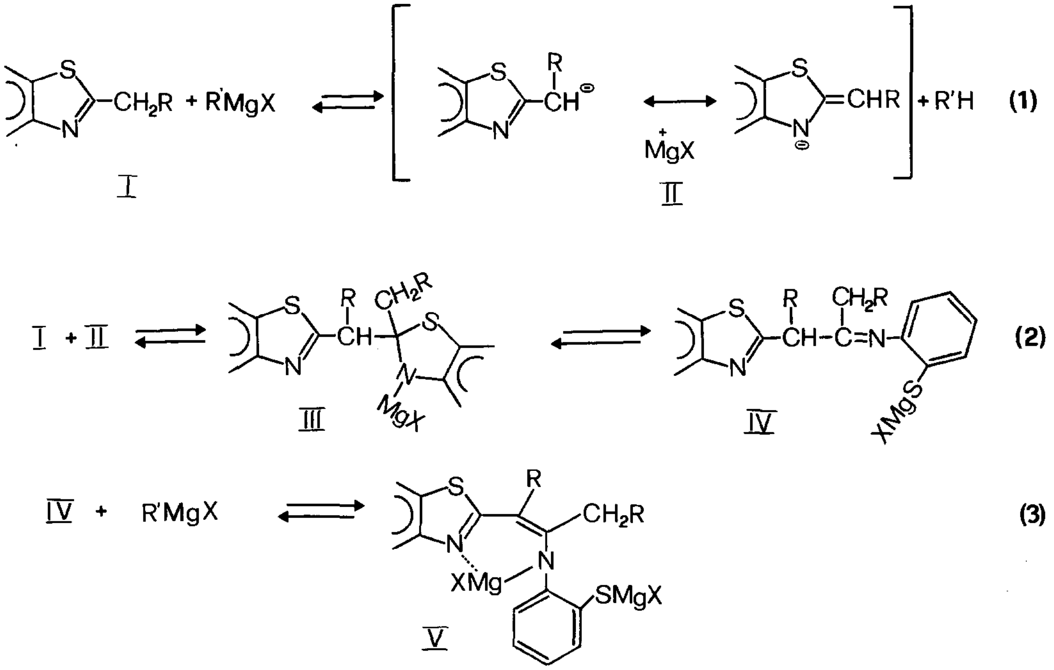
In the preceding paper we have described a novel ring opening reaction of benzothiazoles with allylic Grignard reagents.[1] The reaction was specific of allylic Grignards, as we found that benzothiazole did not react with n-BuMgBr and treatment with PhMgBr afforded an intractable mixture of many products. In order to understand the different behaviour of alkyl and aryl Grignard reagents with respect to the allylic derivatives, we started a more detailed investigation of the reaction of some benzothiazoles and alkyl and aryl Grignard reagents.

The addition of phenylmagnesium bromide (2.2 mole) to a THF solution of 2-methylbenzothiazole 1a (1 mole) resulted in a dark red solution. Quenching with methyl iodide after 8 h at reflux and usual workup furnished a yellow crystalline compound that was characterized by elemental analysis and ^{1}HNMR, ^{13}CNMR and Mass spectroscopy.[2] The ^{1}HNMR spectrum showed a broad signal (δ 11.3) that exchanged rapidly with D_2O and a vinylic proton (δ 5.4) that exchanged much more slowly (overnight) in the presence of D_2O. The ^{13}CNMR spectroscopy indicated the presence of 17 carbons and the Mass spectrum revealed a $M^+/e = 312$. On the basis of these results we conclude that the compound must have the structure of 2a.



1a	R = H	2a
1b	R = CH_3	2b
1c	R = Ph	2c
1d	R = CH_2CH_3	2d

Similarly,2-alkylbenzothiazoles **1b**, **1c** and **1d**[3] reacted with phenylmagnesium bromide to furnish high yields of compounds **2b**, **2c** and **2d** respectively.[2] Comparable results were obtained with ethylmagnesium bromide and n-butylmagnesium bromide. It is worth mentioning that the reaction of **1c** with PhMgBr followed by quenching with methyl iodide afforded α-phenylethylbenzothiazole **3**[4] as a by-product. Moreover,the evolution of a quantitative amount of butane was observed in the reaction of **1a** with n-BuMgBr. These findings seemed to indicate that the Grignard reagent behaved as a base. Therefore,a possible mechanism that may account for the formation of compounds **2a-d** could be that accepted for the Claisen condensation of esters[5] and carboxamides,[6] as that illustrated in the scheme below. The first step involves the metallation of the alkyl group in the 2-position of I to give II. Accordingly,a hydrogen deuterium exchange experiment furnished evidence for the incorporation of deuterium (~70%) in the methylene group in the 2-position of **1c** recovered after treatment with PhMgBr and quenching with D_2O before com-



pletion of the reaction.[7] A further support for the formation of the carbanionic species II comes from the isolation of **3** in the reaction of **1c** with PhMgBr followed by addition of MeI. In the second step the carbanionic species II would lead a nucleophilic attack on the C-N double bond of I to generate the benzothiazole-benzothiazoline intermediate III that would then undergo ring opening to furnish IV.The third step is the driving force of the whole process in which the ring opened compound IV is rapidly converted into V which is strongly stabilised by chelation into the six-membered cyclic structure V. The metal must be playing an important role in this reaction and we believe that the good complexing ability of magnesium[8] is crucial in promoting self-condensation as other strong bases such as t-BuOK and KH in THF are not effective and the use of n-BuLi as condensing agent for benzothiazole 1a produced a mixture of several products among which self-condensed compound 2a in low yield.[9]

It is worth noting that when the reaction of 1a with PhMgBr was quenched with aqueous ammonium chloride the TLC clearly indicated the complete disappearance of the starting material and the presence of just one new product substantially. However, when we tried to purify it by column chromatography we recovered the starting benzothiazole 1a almost quantitatively. A possible explanation for this might be the reversibility of the self-condensation reaction under these experimental conditions.

Conclusively, 2-alkylbenzothiazoles having hydrogens on the carbon in the 2-position undergo clean Claisen-type self-condensation. We wish to emphasize that this is the first example of self-condensation of benzothiazoles to be reported, albeit the 2-alkylbenzothiazoles have been reacted with Grignard reagents[10] and organolithium[11] but to give quite different reaction products. The present reaction can be conveniently used to synthesize novel benzothiazole derivatives such as 2 that are expected to show great coordinating properties.

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

References

1) F. Babudri, G. Bartoli, F. Ciminale, S. Florio and G. Ingrosso, Tetrahedron Lett., preceding paper.

2) Typical experimental conditions were those described for the reaction of 1a. To a solution of 1a (0.5 g, 33 mmole) in 20 ml of THF was added PhMgBr (70 mmole) under nitrogen with stirring. The reaction mixture was refluxed for 8 h and then an excess MeI was added. Usual workup gave the self-condensed product 2a. The new compounds showed the following data: 2a, 95% yield, m.p. 98-99°C (ethanol). Elemental analysis, Calc.: C%, 65.4; H%, 5.1; N%, 9.0. Found: C%, 65.7; H%, 5.1; N%, 9.1. Mass(70eV) M^{+}/e= 312. ^{1}HNMR (CDCl$_3$): δ 2.0 (s, 3H), 2.4 (s, 3H), 5.4 (s, 1H, exchanges slowly with D$_2$O), 7.0-7.8 (m, 8H), 11.3 (bs, 1H, exchanges rapidly with D$_2$O). ^{13}CNMR (CDCl$_3$): δ 15.5, 20.1, 91.7, 120.6, 120.9, 122.9, 125.4, 125.6, 125.8, 126.2, 126.7, 132.5, 135.2, 138.0, 150.3, 154.0, 167.3. 2b, 85% yield, m.p. 114-115° C (ethanol). ^{1}HNMR (CDCl$_3$): δ 1.0 (m, 6H), 2.2 (s, 3H), 2.4 (s, 3H), 2.1-2.6 (m, 2H), 7.0-7.8 (m, 8H), 12.8 (bs, 1H, exchanges with D$_2$O). 2c, 45% yield, thick oil, ^{1}HNMR (CDCl$_3$): δ 2.3 (s, 3H), 3.5 (s, 2H), 6.6-7.7 (m, 13H), 12.0 (bs, 1H, exchanges with D$_2$O). 2d, 90% yield, thick oil. ^{1}HNMR (CDCl$_3$): δ 0.8 (m, 6H), 1.2 (m, 4H), 2.2 (s, 3H), 2.4 (q, 2H), 6.8-7.7 (m, 8H), 11.9 (bs, 1H, exchanges with D$_2$O).

3) Compounds **1b**, **1c** and **1d** were prepared by cyclisation of o-aminothiophenol with the appropriate acyl chloride.

4) Compound **3**, that forms in the reaction of **1c** with PhMgBr (45% yield), shows: oil. ^{1}HNMR (CDCl$_3$): δ 1.8 (d, 3H, J 9Hz), 4.4(q, 1H, J 9Hz), 6.9-7.9 (m, 9H).

5) C.R. Hauser and B.E. Hudson, *Organic Reactions*, vol. 1, p. 262. Wiley, New York (1947).

6) F. Babudri, F. Ciminale, L. Di Nunno and S. Florio, *Tetrahedron*, **38**, 557 (1982).

7) No deuterium incorporation at the methyl group of **1a** was detected. Evidently, in this case the carbanionic species does not accumulate so to be trapped in the reaction medium.

8) "*Stability of metal-ion Complexes*", The Chemical Society, London, 1964.

9) A likely explanation for the better condensing ability of Grignards with respect to n-BuLi may be the higher stability of the metal chelate of magnesium than that of the lithium analogue, in accordance with the stability costants reported for metal acetylacetonates. See ref. 8.

10) I.N. Somin, *Zh.Obshch.Khim.*, **39**, 1854 (1969); B.E. Gruz, L.I. Katerinenko and L.M. Yagupol'skii, *ibid.*, **37**, 2029 (1967).

11) E.J. Corey and D.L. Boger, *Tetrahedron Lett.*, 5 (1978).

(Received in UK 27 February 1984)