Tetrahedron Vol. 41, No. 15, pp. 3091 to 3094, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00

GRIGNARD REAGENT INDUCED SELF-CONDENSATION OF BENZOXAZOLES: SYNTHESIS OF BENZOXAZOLYLALKYL ALKYL KETONES.

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(*Received in UK* 23 *April* 1985)

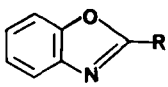
Abstract. 2-Alkylbenzoxazoles 1 undergo clean Claisen-type self-condensation upon treatment with n-BuMgBr and quenching with aqueous NH_4Cl to give 5. In contrast, quenching of the reaction with aqueous HCl furnishes quite good yields of the benzoxazolylalkyl alkyl ketones 8.

In a recent paper[1] we have reported on the Grignard reagent promoted Claisen-type self-condensation of 2-alkylbenzothiazoles. The reaction, that involved metallation at the alkyl group and subsequent addition to the C-N double bond of the thiazole moiety, turned out to be a useful route for the functionalisation of the benzothiazole system.

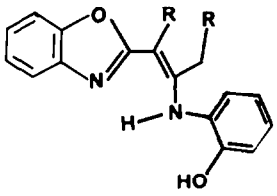
As part of a program aimed at preparing novel functionalised benzo-X-azoles[2] we reasoned that new benzoxazole derivatives might be obtained by self-condensation of the easily available 2-alkylbenzoxazoles. Moreover, what prompted us to try this was the fact that, despite the extensive literature pertaining the metallation of the oxazole derivatives,[3] no self-condensation of 2-alkylbenzoxazoles had ever been reported. The present paper reports the results of the investigation of the reaction of some 2-alkylbenzoxazoles and n-butylmagnesium bromide.

When a THF solution of 1a was refluxed with n-butylmagnesium bromide for about 8h and the brown reaction mixture was quenched with aqueous ammonium chloride, the usual work-up gave a solid residue that was (TLC) substantially one compound, further purified by crystallisation from petroleum ether.[4] This compound had the structure 5a, as ascertained by elemental analysis, IR and ^{1}H-NMR spectroscopy. In a similar fashion the benzoxazoles 1b-e reacted with n-BuMgBr providing high yields of the products 5b-e.

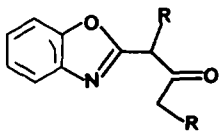
A plausible mechanism that may account for the formation of the products 5 is outlined in Scheme I and involves, as in the case of the reported self-condensation of 2-alkylbenzothiazoles,[1] the metallation at the alkyl group in the 2-position of the benzoxazole derivative 1 to give 2. Subsequent addition of 2 to the C-N double bond of 1 would produce 3, which is rapidly converted into 4, strongly stabilised by chelation.



1a: R= Me
1b: R= Et
1c: R= Pr^n
1d: R= Bu^n
1e: R= Bz
1f: R= Pr^i

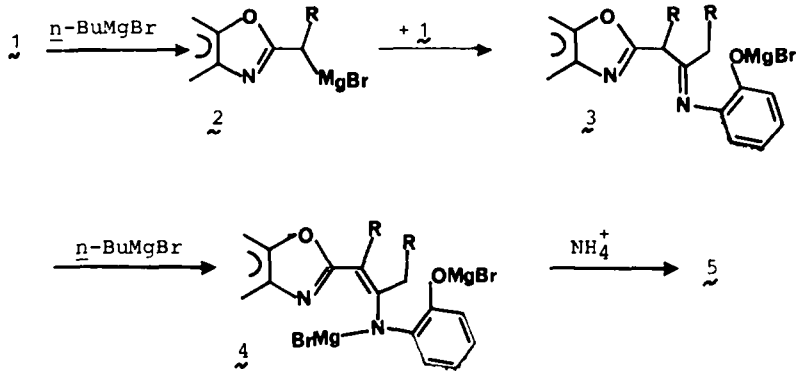


5a: R= H
5b: R= Me
5c: R= Et
5d: R= Pr^n
5e: R= Ph



8a: R= H
8b: R= Me
8c: R= Et
8d: R= Pr^n

SCHEME I

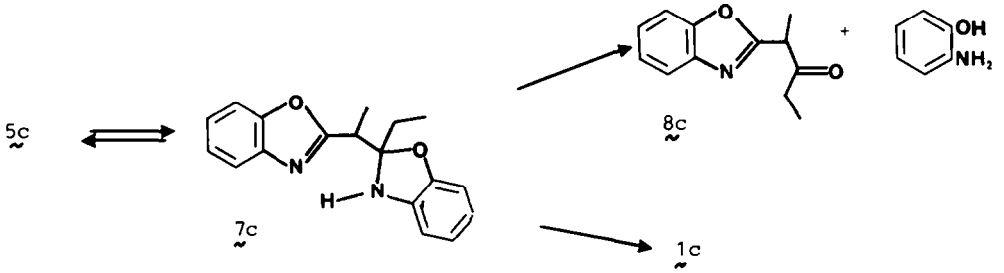


It was interesting to note that the self-condensed compounds 5, although stable in the solid state, slowly decompose in $CDCl_3$ solution. Indeed, the ^{1}H-NMR spectrum of 5c, registered soon after solving the sample in $CDCl_3$, showed, accordingly with the assigned structure, the presence of two broad singlets at 6.6 and 10.6 ppm which exchanged with D_2O. The spectrum of the same compound 5c, registered 1h after solving it in $CDCl_3$, clearly indicated the disappearance of the singlet at 6.6 ppm (OH) and the presence of other species together with 5c. The IR spectrum of this solution showed a carbonyl stretching absorption at 1720 cm^{-1} and the NH stretching at 3470 cm^{-1}. Moreover, a new ^{1}H-NMR spectrum recorded about three days later clearly showed the presence of the starting benzoxazole 1c. A plausible rationalisation of these results might be that the small amount of DCl which is present in $CDCl_3$[5] catalyzes the conversion of the self-condensed product 5c to 1c, via the benzoxazolebenzoxazoline 7c, which on the other hand may undergo the benzoxazoline ring cleavage to give the ketone 8c and the o-aminophenol, as in Scheme II. Accordingly, the addition of a solution of DCl/D_2O to the NMR tube containing the $CDCl_3$ solution of 5c greatly accelerated the abovementioned decomposition. Still in agreement with this hypothesis, when the reaction between 1c and n-BuMgBr was quenched with aqueous 1N HCl the ketone 8c formed in a very good yield. Evidently, the acidic medium strongly promotes the conversion of 7c into 8c. Similarly, the reaction of benzoxazoles 1a, 1b and 1d with n-BuMgBr and subsequent quenching with HCl afforded ketones 8a, 8b and 8d respectively.

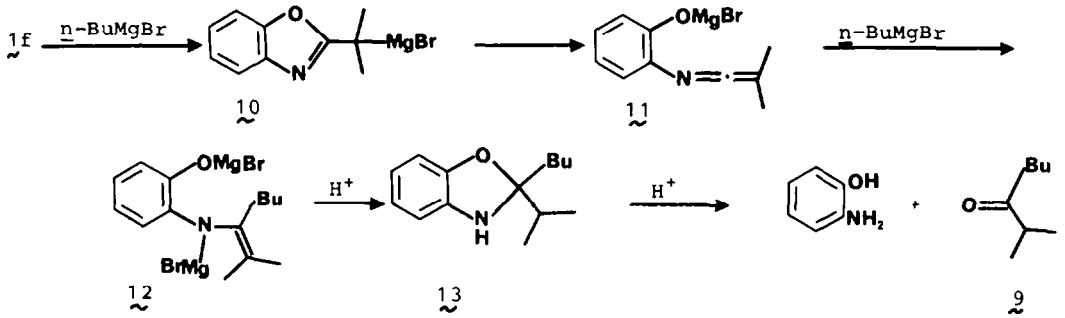
Attempted self-condensation of the isopropylbenzoxazole 1f was not successful. Indeed, the reaction of 1f with n-BuMgBr and quenching with NH_4Cl led mainly to

the starting benzoxazole together with some o-aminophenol and the butyl isopropyl ketone 9. This result may be explained, accordingly with what suggested by Meyers for oxazolines,[6] by the slow rate of tertiary proton removal followed by rearrangement of the α carbanion 10 to the ketenimine 11 and addition of unreacted n-BuMgBr leading to 12. Then, ring closure of 12 to the benzoxazoline 13 and hydrolysis would give the o-aminophenol and the ketone 9, as shown in Scheme III. Alternatively one may hypothesize direct attack of n-BuMgBr to the C=N of 1f to give 13, although it has been reported that Grignards add reluctantly to the C-N double bond of oxazolines.[7]

SCHEME II



SCHEME III



In conclusion, 2-alkylbenzoxazoles, like 2-alkylbenzothiazoles, undergo self-condensation under basic conditions with n-BuMgBr. The reaction appears to be useful from the synthetic viewpoint as it allows the preparation of functionalised benzoxazoles such as self-condensed compounds 5 and the benzoxazolylalky alkyl ketones 8.

Experimental

^{1}H-NMR spectra were recorded on a Varian EM 360A or a Varian XL200 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. Satisfactory analytical data (± 0.3 for C,H,N) were observed for all the new compounds.

Materials. Tetrahydrofuran (THF) from commercial source (RS, Carlo Erba) was purified by distillation (twice) from sodium wire in a N_2 atmosphere. All other chemicals were commercial grade and were purified by distillation or crystallisation prior to use. 2-Methyl- 1a, 2-n-propyl- 1c, 2-i-propyl- 1f, 2-n-butyl-benzoxazole 1d were prepared according to the procedure reported[8] for 2-ethyl- 1b and 2-benzyl-benzoxazole 1e from o-aminophenol and the appropriate acyl chloride.

Reaction of benzoxazoles 1a-g with n-BuMgBr and quenching with aqueous NH_4Cl:General Procedure. The reaction of benzoxazole 1a is described as an example. A stirred solution of 1a (0.258 g,

1.98 mmole) in 25 ml of dry THF was refluxed with n-BuMgBr (2.97 mmole) for about 8h under a nitrogen atmosphere. Then the brown reaction mixture was quenched with sat aqueous NH_4Cl (10 ml), extracted with ether (3 x 25 ml); dried over $MgSO_4$ and the solvent was removed under reduced pressure leaving a solid residue that was purified by crystallisation from petroleum ether (60-80° boiling fraction). IR and ^{1}H-NMR data are given below.

1-(2-benzoxazolyl)-2-(o-hydroxyanilino)propene 5a: 95% yield, mp 142-143°C (60-80° petroleum ether); IR(nujol): 3490 (broad band, OH and NH) cm^{-1} ^{1}H-NMR ($CDCl_3$):δ 1.9 (s, 3H), 5.4 (s, 1H), 6.0 (bs, OH, exchange with D_2O), 6.9-7.7 (m, 8H), 10.0 (bs, NH, exchange with D_2O).

2-(2-benzoxazolyl)-3-(o-hydroxyanilino)-2-pentene 5b: 96% yield, mp 109-110°C (60-80° petroleum ether); IR (nujol) 3500-3100 (broad band, OH and NH) cm^{-1}; ^{1}H-NMR ($CDCl_3$)(imine-enamine tautomerism): enamine form 5b (75%): δ 1.05 (t, 3H, J=7Hz), 1.6 (q, 2H, J=7Hz), 2.2 (s, 3H), 6.3 (bs, OH, exchange with D_2O), 6.8-7.7 (m, 8H), 10.6 (bs, NH, exchange with D_2O); imine form (25%): δ 1.05 (t, 3H, J=7Hz), 1.85 (q, 2H, J=7Hz) 2.42 (d, 3H, J=7Hz), 3.7 (q, 1H, J=7Hz); 6.3 (bs, OH, exchange with D_2O), 6.8-7.7 (m, 8H).

3-(2-benzoxazolyl)-4-(o-hydroxyanilino)-3-heptene 5c. 93% yield, mp 99-101°C (60-80° petroleum ether); IR (nujol): 3500-3400 (broad band, OH and NH) cm^{-1}; ^{1}H-NMR ($CDCl_3$):δ 0.8-1.7 (m, 8H), 2.1-2.8 (m, 4H), 6.6 (bs, OH, exchange with D_2O), 6.8-7.8 (m,8H), 10.7 (bs, NH, exchange with D_2O).

4-(2-benzoxazolyl)-5-(o-hydroyanilino)-4-nonene 5d: 90% yield, mp 99-101°C (60-80° petroleum ether); ^{1}H-NMR ($CDCl_3$):δ 0.8-2.0 (m, 12H), 2.2-2.8 (m, 4H), 6.5 (bs, OH, exchange with D_2O), 6.8-7.9 (m, 8H), 10.7 (bs, NH, exchange with D_2O).

1-(2-benzoxazolyl)-1,3-diphenyl-2-(o-hydroxyanilino) propene 5e: 92% yield, mp 123-125°C (60-80° petroleum ether); IR (nujol): 3400-3300(broad band, OH and NH) cm^{-1}; ^{1}H-NMR ($CDCl_3$):δ 3.7 (s, 2H), 5.7 (bs, OH, exchange with D_2O), 6.8-7.8 (m, 18H), 11.0 (bs, NH, exchange with D_2O).

Reaction of benzoxazoles 1a-d with n-BuMgBr and quenching with aqueous HCl. The reaction of 1a is described ad an example. 0.5 g (3.75 mmole) of 1a were reacted with n-BuMgBr (5.6 mmole) as above. After 8h the brown reaction mixure was quenched with 10 ml of aqueous 1N HCl. Extraction with ether (3 x 25 ml), washing with $NaHCO_3$ (2 x 20 ml), drying over $MgSO_4$ and removal of the solvent under reduced pressure gave 8a as a crystalline compound. IR and ^{1}H-NMR data are reported below.

2-Benzoxazolylpropanone 8a:63% yield, mp 71-73°(ether); IR (nujol): 1720 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): carbonyl form (85%):δ 2.4 (s, 3H), 4.2 (s, 2H), 7.4-8.0 (m, 4H); enol form (15%):δ 2.2 (s, 3H), 5.6 (s, 1H), 7.4-8.0 (m, 4H).

2-(2-Benzoxazolyl)-3-pentanone 8b: 93% yield, oil; IR (neat): 1730 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$); carbonyl form (~85%): δ 0.9 (t, 3H, J=7Hz), 1.7 (d, 3H, J=7Hz), 2.5 (q, 2H, J=7Hz), 4.1 (q, 1H, J=7Hz), 7.2-7.9 (m, 4H); enol form (~15%):δ 0.9 (t, 3H, J=7Hz), 2.0 (s, 3H), 2.8 (q, 2H, J=7Hz), 7.2-7.9 (m, 4H).

3-(2-Benzoxazoly)-4-heptanone 8c: 93% yield, oil; IR (neat): 1725 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$):δ 1.0 (t, 6H, J=8Hz), 1.3-2.7 (m, 6H), 4.05 (t, 1H, J=8Hz), 7.3-8.0 (m, 4H).

4-(2-Benzoxazolyl)-5-nonanone 8d: 88% yield, oil; IR (neat): 1720 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$):δ 0.8-1.9 (m, 12H), 2.15 (t, 2H, J=8Hz), 2.6 (t, 2H, J=8Hz), 4.25 (t, 1H, J=8Hz), 7.3-8.0 (m, 4H).

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