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RING OPENING OF BENZOXAZOLES WITH ALLYLIC GRIGNARD REAGENTS: SYNTHESIS OF N-DIALLYLALKYL-o-AMINOPHENOLS.

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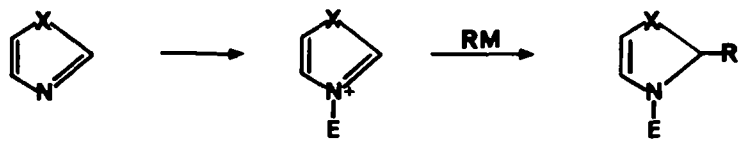
Abstract. The title benzoxales 1a-d react cleanly with allylic Grignard reagents 2a-c undergoing ring opening to give good yields of N-diallyl-alkyl-o-aminophenols 3a-m. A plausible mechanism is discussed.

It is known that Grignard reagents and organolithiums do not add directly to the C-N double bond of thiazole,[1] oxazole[2] and imidazole[3] derivatives. Indeed, for the addition of the organometallic reagent to such a C=N link takes place to give the corresponding azoline, a preliminary quaternisation of the aza group, that renders the 2-carbon much more electrophilic, is necessary (Scheme I).

SCHEME I



X= S,O,N E= alkyl, acyl

However, such an activation, usually accomplished by alkylation[1-3] or acylation,[4] presents some drawbacks as the alkyl group, previously introduced on the aza group, is difficult to be removed and with the acylazolium salts in some cases the organometallic reagent attacks the carbonyl group of the acyl function rather than the 2-carbon atom.[4]

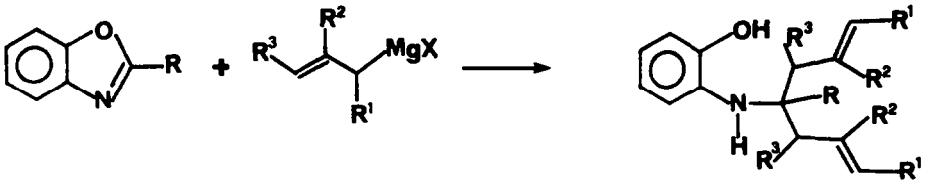
Only quite recently we have discovered that allylic Grignard reagents add directly to the C-N double bond of a large number of benzothiazoles,[5] providing allylbenzothiazoles, allylbenzothiazolines and N-allylalkyl-o-aminobenzenethiols, the formation of which has been rationalised by assuming that the reactions proceed through a cyclic transition state following a preliminary coordination of magnesium of the Grignard reagent on the aza group of the thiazole system.

As an extension of our researches concerning the reactions of Grignards with heterocycles containing the C=N link,[5] we report here the results of the

reaction between some benzoxazole derivatives and allylic Grignard reagents.

RESULTS AND DISCUSSION

Treatment of benzoxazole 1a (1 mole) with 2-propenylmagnesium bromide 2a (2.2 mole) at -15°C and subsequent quenching of the reaction mixture with aqueous ammonium chloride gives a good yield of the ring opened product 3a. Under the same experimental conditions 1a reacts with 2-methyl-2-propenylmagnesium chloride 2b and 2-butenylmagnesium bromide 2c to give the ring opened compounds 3b and 3c respectively. Similarly, benzoxazoles 1b-d react with 2a-c to furnish the N-diallylalkyl-o-aminophenols 3d-m. (See Table).



1a: R=H
1b: R=Me
1c: R=Et
1d: R=Bz

2a: $R^1=R^2=R^3=H$
2b: $R^1=R^3=H$; $R^2=Me$
2c $R^1=R^2=H$; $R^3=Me$

3a: $R=R^1=R^2=R^3=H$
3b: $R=R^1=R^3=H$; $R^2=Me$
3c: $R=R^1=R^2=H$; $R^3=Me$
3d: $R=Me$; $R^1=R^2=R^3=H$
3e: $R=R^2=Me$; $R^1=R^3=H$
3f: $R=R^3=Me$; $R^1=R^2=H$
3g: $R=Et$; $R^1=R^2=R^3=H$
3h: $R=Et$; $R^2=Me$; $R^1=R^3=H$
3i: $R=Et$; $R^3=Me$; $R^1=R^2=H$
3k: $R=Bz$; $R^1=R^2=R^3=H$
3l: $R=Bz$; $R^2=Me$; $R^1=R^3=H$
3m: $R=Bz$; $R^3=Me$; $R^1=R^2=H$

The ring opened compounds 3 form specifically with allylic Grignards since, in agreement with the previous observations that 2-oxazolines[2] were inert to alkyl and aryl Grignards, no reaction occurs under the same experimental conditions with n-BuMgBr and PhMgBr.

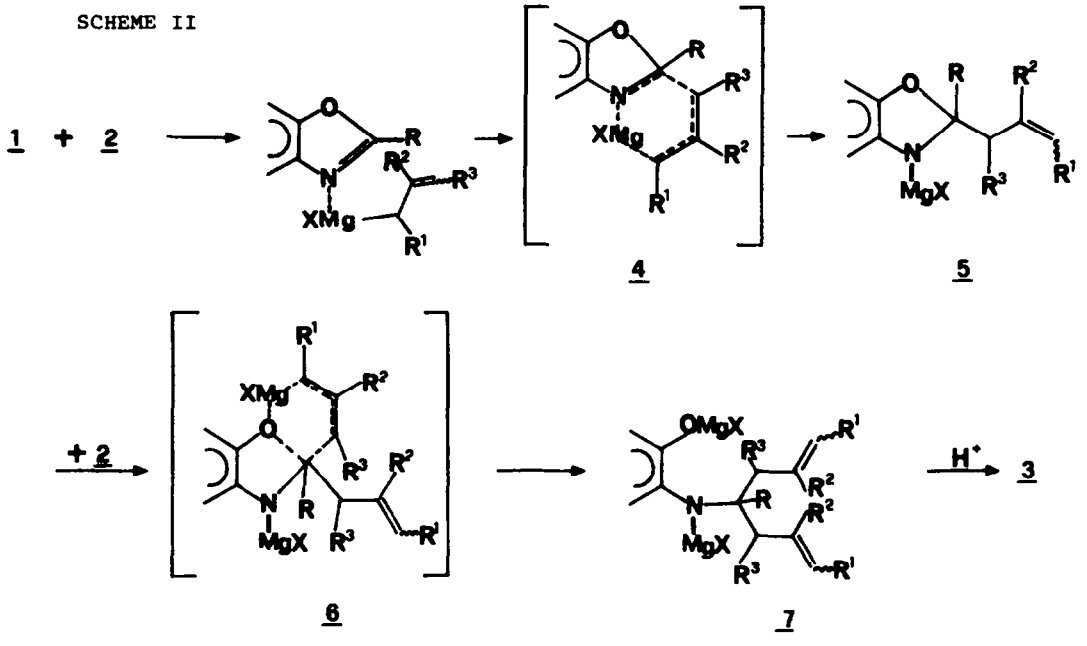
It is worthy noting that the reaction of benzoxazoles 1a, 1b, 1c and 1d with the allylic Grignard reagent prepared from crotyl bromide 2c leads exclusively to the open-chain products 3i, 3k, 3l and 3m respectively in which the allylic groups turn out to be attached through the more substituted carbon.

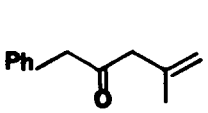
A likely mechanism that may account for the formation of the N-diallylalkyl-o-aminophenols 3 is shown in Scheme II. According to this mechanism, the first stage of the reaction involves the coordination of magnesium on the aza group of the oxazole system that provides activation for the nucleophilic attack of the allylic moiety on the 2-carbon. Also with alkyl and aryl Grignards such a coordination should occur but, as mentioned above, no reaction takes place. Therefore it is li-

kely to think that allylic Grignard reagents do react as they permit a six-membered cyclic transition state such as 4. Then, the benzoxazoline 5 would form as an intermediate, from which the ring opened product 3 would derive by reaction of a second equivalent of the Grignard reagent 2 assisted by the complexation of magnesium on the heterocyclic oxygen atom leading, via the six-membered cyclic transition state 6, to the open-chain salt 7 and after quenching to 3. In agreement with this mechanism, the fact that with the crotylmagnesium bromide 2c the formed ring opened products have the allylic groups bonded through the more substituted carbon may be explained if one considers the bidentate nature of this Grignard reagent in which there exists an equilibrium between the linear and the branched chain forms.[6]

A good support to the mechanism above would come from the isolation of the benzoxazoline 4. However, attempts to isolate 4 by carrying out the reaction using a 1:1 molar ratio between reactants and low temperature failed. In all cases we obtained the open-chain products 3 and unreacted starting material. Specifically in the case of the reaction between 2-benzylbenzoxazole 1d and methallylmagnesium chloride 2b the use of hexamethylphosphoramide (HMPA) in order to minimize the complexation of magnesium on the heterocyclic oxygen,[7] an event that would provide activation for the second nucleophilic attack of the Grignard on the 2-carbon to give 3, led to a mixture of o-aminophenol and ketones 8 and 9.

SCHEME II





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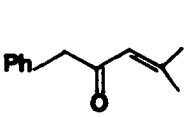
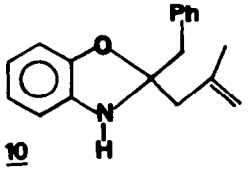


9



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This result clearly indicates that the 2,2-diallylbenzoxazoline 10 actually forms but rapidly decomposes (perhaps during the work-up procedure) undergoing ring opening to give the ketone 8 that may isomerise to the ketone 9.

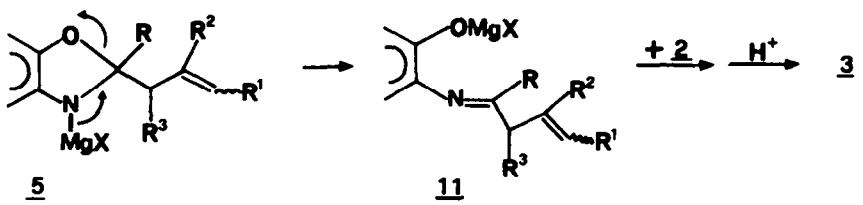
An alternative mechanism for the formation of the ring opened compounds 3 involves the Schiff's base 11, produced by the ring cleavage of 5, and subsequent addition of 2 on its C-N double bond (Scheme III).

TABLE. Reactions of benzoxazoles 1a-d with allylic Grignard reagents 2a-c in tetrahydrofuran.

Benzoxazole	Grignard Reagent	Reactants Molar Ratio	Temperature °C	Product(yield %)[a,f]
1a	2a[c]	1:2.2	-15	3a (70)
"	2b[d]	"	"	3b (69)
"	"	1:2	-60	" (49)[b]
"	2c[c]	1:1	"	3c (28)[b]
"	"	1:2.2	-15	" (73)
1b	2a	"	"	3d (65)
"	"	"	-78	" (45)[b]
"	2b	"	-15	3e (67)
"	2c	"	"	3f (45)
1c	2a	"	"	3g (79)
"	2b	"	"	3h (66)
"	2c	"	"	3i (77)
1d	2a	"	"	3k (85)
"	2b	"	"	3l (87)
"	2c	"	"	3m (78)
"	2b[e]	1:1	"	8 (33)
				9 (66)

a) Yield based on the starting material and determined on isolated purified products; b) Also some unreacted starting material was recovered; c) Grignard reagent prepared in ether; d) Grignard reagent prepared in THF; e) Reaction carried out in the presence of HMPA (2:1 molar ratio with respect to the Grignard reagent); f) All new compounds gave satisfactory microanalytical data for C, H, and N.

SCHEME III



5 11

More work is needed for the mechanism to be clarified, however, whatever it

is, the present ring opening reaction of benzoxazoles is of interest from the synthetic viewpoint as the novel N-diallylalkyl-o-aminophenols 3 may be used for the synthesis of functionalised and more complex heterocyclic systems.Moreover, finding the suitable conditions to stop the reaction of 1 with 2 to the allylalkylbenzoxazolines would open a convenient route to allylalkylketones by following the ketone-oxazoline Meyers's procedure.[8]

In conclusion, we wish to point out that benzoxazoles, like benzothiazoles, do react with allylic Grignard reagents undergoing ring opening and this must be ascribed either to the fact that the coordination of magnesium on the aza group or on the ring oxygen makes the 2-carbon more electrophilic and that the allylic moiety, due to its bidentate reagent nature, allows a six-membered cyclic transition state that other Grignards cannot give. Moreover, such a property of the allylic Grignard reagents might be used for the functionalisation of the 2-carbon of benzoxazoles if a good leaving group is present in that position.

Experimental

^{1}H NMR spectra were recorded on a Varian EM 360A 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.

Materials. Tetrahydrofuran (THF) and diethyl ether from commercial sources (RS, Carlo Erba) were purified by distillation (twice) from sodium wire in a N_2 atmosphere. Benzoxazole 1a (Janssen) was purified by distillation. All other chemicals were commercial grade and were purified by distillation or crystallisation prior to use. 2-Methyl-,[9] 2-ethyl-,[9] and 2-benzyl-benzoxazole[9] were prepared according to the reported procedure. 2-Propenylmagnesium bromide in ether and 2-methyl-2-propenylmagnesium chloride in THF were prepared as reported for 1-methyl-2-propenylmagnesium bromide in ether.[10]

Reaction of benzoxazoles 1a-d with allylic Grignard reagents 2a-c: General procedure. The reaction of benzoxazole 1a with 2a is described as an example. To a stirred solution of 1a(1g, 8.2 mmole) in THF (25 ml) was added the appropriate number of moles of 2a (0.6 N) under a nitrogen atmosphere. The resulting brown solution was stirred at the given temperature up to the disappearance of the starting material or as long as TLC showed no further change. Then the mixture was quenched with sat aqueous NH_4Cl (30 ml), extracted with ether (3 x 25 ml), dried over $MgSO_4$ and the ether was removed under reduced pressure. The reaction products were purified or separated by column chromatography (silica gel, ether/petrol 1:1). IR and NMR data are given below.

N-(di-2-propenyl)methyl-o-aminophenol 3a. Oil; ^{1}H NMR ($CDCl_3$): δ 2.2-2.5 (m, 4H), 3.3-3.8 (m, 1H), 4.7 (s, 1H, exchange with D_2O), 5.0-5.35 (m, 4H), 5.5-6.3 (m, 2H), 6.5-7.2 (m, 5H, 1 OH, exchange with D_2O).

N-(di-2-methyl-2-propenyl)methyl-o-aminophenol 3b. Oil; IR(neat): 3540-3140(broad band, OH and NH) and 1650(C=C) cm^{-1}. ^{1}H NMR($CDCl_3$ + D_2O): δ 1.8 (s, 6H), 2.3 (d,4H), 4.8 (s,4H), 6.7-7.1 (m, 4H).

N-(di-1-methyl-2-propenyl)methyl-o-aminophenol 3c. Oil; IR(neat): 3520-3160(broad band, OH and NH) and 1635(C=C) cm^{-1}. ^{1}H NMR($CDCl_3$ + D_2O): δ 1.05 (d, 6H), 2.3-2.8 (m, 2H), 3.0-3.4 (m, 1H), 4.9-5.3 (m, 4H), 5.6-6.2 (m, 2H), 6.5-7.2 (m, 4H).

N-(di-2-propenyl)ethyl-o-aminophenol 3d. Oil; ^{1}H NMR($CDCl_3$): δ 1.1 (s, 3H), 2.3 (d, 4H),5.0-6.3 (m, 8H, 1 OH and 1 NH, exchange with D_2O), 6.8-7.2 (m, 4H).

N-(di-2-methyl-2-propenyl)ethyl-o-aminophenol 3e. Oil; IR(neat): 3520-3200(broad band, OH and NH) and 1645(C=C) cm^{-1}. ^{1}H NMR($CDCl_3$ + D_2O): δ 1.25 (s, 3H), 1.9 (s, 6H), 2.4 (s, 4H), 4.8-5.2 (m, 4H), 6.8-7.2 (m, 4H).

N-(di-1-methyl-2-propenyl)ethyl-o-aminophenol 3f. Oil; IR(neat): 3560-3140(broad band, OH and NH) and 1640(C=C) cm^{-1}. ^1H NMR($CDCl_3$ + D_2O): δ 1.1 (s, 3H), 1.2 (s, 6H), 2.4-3.0 (m, 2H), 5.0-5.4 (m, 4H),5.8-6.4 (m, 2H), 6.7-7.3 (m, 4H).

N-(di-2-propenyl)-n-propyl-o-aminophenol 3g. Oil; IR(neat): 3540-3200(broad band, OH and NH) and 1640(C=C) cm^{-1}. ^1H NMR($CDCl_3$ + D_2O): δ 0.9 (t, 3H), 1.65 (q, 2H), 2.35 (d, 4H), 5.0-5.4 (,m, 4H),5.6-6.3 (m, 2H), 6.8-7.2 (m, 4H).

N-(di-2-methyl-2-propenyl)-n-propyl-o-aminophenol 3h. Oil; IR(neat): 3520-3160 (broad band, OH and NH) and 1640(C=C) cm^{-1}. ^1H NMR($CDCl_3$ + D_2O): δ 0.9 (t, 3H), 1.7 (q, 2H), 1.8 (s, 6H), 2.4 (s, 4H), 4.8-5.1 (m, 4H), 6.5-7.2 (m, 4H).

N-(di-1-methyl-2-propenyl)-n-propyl-o-aminophenol 3i. Oil; ^1H NMR($CDCl_3$): δ 0.9 (t, 3H), 1.1 (d, 6H), 1.6-2.0 (m, 2H), 2.5-3.0 (m, 2H), 3.6-4.8 (broad peak, 2H, 1 OH and 1 NH, exchange with D_2O), 4.9-5.3 (m, 4H), 5.8-6.5 (m, 2H), 6.7-7.2 (m, 4H).

N-(di-2-propenyl)phenylmethyl-o-aminophenol 3k. Oil; IR(neat): 3540-3160(broad band, OH and NH) and 1640(C=C) cm^{-1}. ^1H NMR($CDCl_3$ + D_2O): δ 2.35 (d, 4H), 2.95 (s, 2H), 5.0-5.4 (m, 4H), 5.7-6.4 (m, 2H), 6.8-7.5 (m, 9H).

N-(di-2-methyl-2-propenyl)phenylmethyl-o-aminophenol 3l. Oil; IR(neat): 3540-3160 (broad band, OH and NH) and 1640(C=C) cm^{-1}. ^1H NMR($CDCl_3$ + D_2O): δ 1.9 (s, 6H), 2.5 (s, 4H), 3.2 (s, 2H), 5.0-5.2 (m, 2H), 6.8-7.5 (m, 9H).

N-(di-1-methyl-2-propenyl)phenylmethyl-o-aminophenol 3m. Oil; IR(neat): 3540-3160 (broad band, OH and NH) and 1635(C=C) cm^{-1}. ^1H NMR($CDCl_3$ + D_2O): δ 1.2 (d, 6H), 2.7-3.2 (m, 2H), 3.3 (s, 2H), 4.9-5.4 (m, 4H), 5.6-6.5 (m, 2H), 6.7-7.6 (m, 9H).

4-Methyl-1-phenyl-4-penten-2-one 8. IR(neat): 1720(C=O) and 1650(C=C) cm^{-1}. ^1H NMR (CCl_4): δ 1.7 (s, 3H), 3.1 (s, 2H), 3.65 (s, 2H), 4.8 (s,1H), 4.9 (s, 1H), 7.3 (s, 5H).

4-Methyl-1-phenyl-3-penten-2-one 9. IR(neat): 1685(C=O) and 1620(C=C) cm^{-1}. ^1H NMR (CCl_4): δ 1.9 (s, 3H), 2.2 (s, 3H), 3.6 (s, 2H), 6.0-6.1 (m, 1H), 7.3 (s, 5H).

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Elemental analyses

Compound	Molecular Formula	Calcd. C%	Calcd. H%	Calcd. N%	Found C%	Found H%	Found N%
3a	$C_{13}H_{17}NO$ (203)	76.8	8.4	6.9	76.6	8.3	6.8
3b	$C_{15}H_{21}NO$ (231)	77.9	9.1	6.1	77.8	9.2	6.3
3c	$C_{15}H_{21}NO$ (231)	"	"	"	77.6	9.0	6.2
3d	$C_{14}H_{19}NO$ (217)	77.4	8.8	6.5	77.2	8.7	6.4
3e	$C_{16}H_{23}NO$ (245)	78.4	9.4	5.7	78.5	9.3	5.6
3f	$C_{16}H_{23}NO$ (245)	"	"	"	78.6	9.2	5.4
3g	$C_{15}H_{21}NO$ (231)	77.9	9.1	6.1	77.7	9.0	6.2
3h	$C_{17}H_{25}NO$ (259)	78.8	9.7	5.4	78.6	9.5	5.5
3i	$C_{17}H_{25}NO$ (259)	"	"	"	78.7	9.6	5.6
3k	$C_{20}H_{23}NO$ (293)	81.9	7.8	4.8	81.7	7.8	4.9
3l	$C_{22}H_{27}NO$ (321)	82.2	8.4	4.4	82.3	8.2	4.5
3m	$C_{22}H_{27}NO$ (321)	"	"	"	82.4	8.5	4.3