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CROSS-COUPLING OF 2-CHLOROBENZOXAZOLE WITH β,γ-UNSATURATED GRIGNARD REAGENTS: REGIOSELECTIVE SYNTHESIS OF 2-ALLYL-, 2-ALLENYL-, AND 2-PROPARGYL-BENZOXAZOLES.

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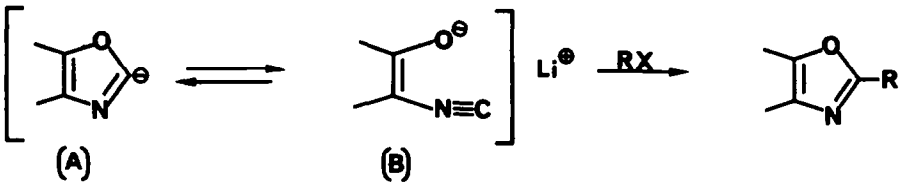
Abstract: β,γ-unsaturated Grignard reagents react regioselectively with 2-chlorobenzoxazole to give high to excellent yields of 2-allyl-, 2-allenyl-, and 2-propargyl-benzoxazoles. Reduction of 2-allylbenzoxazoles leads to quantitative yields of branched 2-alkylbenzoxazoles.

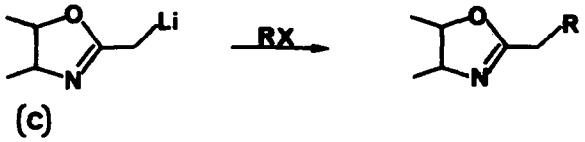
The increasing utility of 2-substituted oxazole derivatives as precursors of more complex heterocycles and for use as latent functional group equivalents is documented in numerous reports.[1]

A useful method of synthesizing 2-alkylsubstituted oxazoles, which does not involve forming the oxazole ring, is by alkylation of the lithiated precursors (A)[2] and (C).[3]

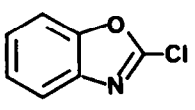
However, such syntheses present some drawbacks due to the equilibrium between the lithiated oxazole (A) and the open-chain tautomer (B)[2], and the presence of acidic hydrogens in the alkylating agent or in the oxazole moiety.[4] Moreover, no secondary or tertiary alkyl group can be introduced in 2-position following the procedure above.

An alternative route to 2-alkylsubstituted oxazoles is by cross-coupling of 2-methylthio oxazole derivatives with Nickel- or Palladium-phosphine complex activated Grignard reagents.[1] However such a procedure applies exclusively to aryl and primary alkyl Grignard reagents. The propensity of the secondary and tertiary alkyl Grignard reagents for undergoing β-elimination[5] and isomerization[6,7] in the presence of Ni(II) or Pd(II) complexes is known.

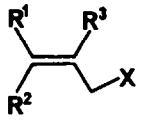




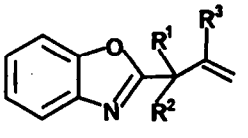
The direct introduction of secondary and tertiary alkyl groups and unsaturated organic groups in the 2-position of oxazoles and benzoxazoles via cross-coupling of 2-heterosubstituted derivatives with the appropriate Grignard reagent has never been reported so far. We now report that we can prepare cleanly and in excellent yields 2-allyl-, 2-allenyl-, 2-propargyl- and branched 2-alkyl--benzoxazoles from readily available 2-chlorobenzoxazole and β,γ-unsaturated Grignard reagents.



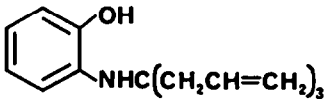
1



2a: $R^1=R^2=R^3=H$; X=Br
2b: $R^1=R^2=H$; $R^3=Me$; X=Cl
2c: $R^1=Me$; $R^2=R^3=H$; X=Br
2d: $R^1=Ph$; $R^2=R^3=H$; X=Cl
2e: $R^1=R^2=Me$; $R^3=H$; X=Cl
2f: $R^1=Me$; $R^2=CH_2CH_2CH=C(CH_3)_2$; $R^3=H$; X=Cl



4a: $R^1=R^2=R^3=H$
4b: $R^1=R^2=H$; $R^3=Me$
4c: $R^1=Me$; $R^2=R^3=H$
4d: $R^1=Ph$; $R^2=R^3=H$
4e: $R^1=R^2=Me$; $R^3=H$
4f: $R^1=Me$; $R^2=CH_2CH_2CH=C(CH_3)_2$; $R^3=H$



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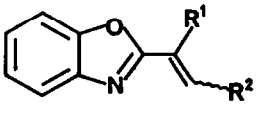
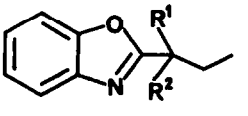
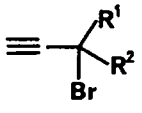


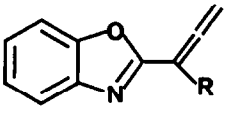
5a: $R^1=R^2=Me$
5b: $R^1=Ph$; $R^2=Me$



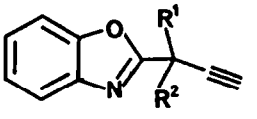
6a: $R^1=H$; $R^2=Me$
6b: $R^1=R^2=Me$



7a: $R^1=R^2=H$
7b: $R^1=H$; $R^2=Me$
7c: $R^1=R^2=Me$



8a: R=H
8b: R=Me



9a: $R^1=R^2=H$
9b: $R^1=H$; $R^2=Me$
9c: $R^1=R^2=Me$

Initial work was centered on the reaction between 2-chlorobenzoxazole 1 and allylmagnesium bromide. Addition of an ether solution of the allylmagnesium bromide (1.94 equiv) to an ether solution of 1 (1 equiv) at room temperature for 30 min produced a deep yellow, homogeneous reaction mixture. Quenching with aqueous sat. ammonium chloride led to the ring opened product 3[8] in 35% yield. Repeating the reaction at 0°C by adding an ether solution of allylmagnesium bromide (1.5 equiv) to a solution of 1 in CH_2Cl_2[9] afforded a mixture of 3 (15%) and the 2-allylbenzoxazole 4a (26%). Lowering the temperature (-75°C) favored the formation of the cross-coupled product 4a (62%).

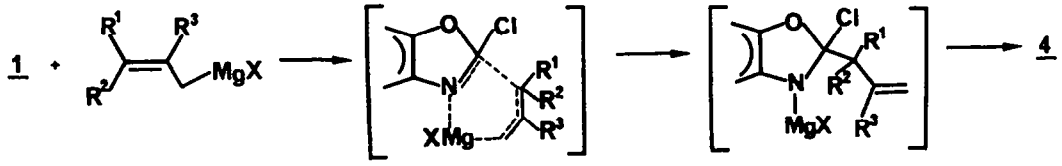
Extending this simple reaction to other allylic Grignards allowed us to obtain excellent yields of the cross-coupled products 4 as shown in Table . The reaction of Grignard reagents prepared from crotyl bromide 2c, cinnamyl chloride 2d, 3,3-dimethylallyl chloride 2e and geranyl chloride 2f proceeded with complete regioselectivity furnishing the cross-coupled products 4c-f in

which the allylic group is attached through the more substituted carbon atom. The allylic Grignards are specific in giving direct cross-coupling with 1, since alkyl and aryl counterparts do not react under comparable experimental conditions.

The cross-coupling of allylic Grignards, in view of their ambident nucleophilic nature may proceed either with a S_Ei' mechanism[10] involving the cyclic transition state (D) (Scheme I), or with a S_E2' mechanism[11] not requiring coordination of magnesium on the aza-group. Accordingly, the formation of the branched allylic benzoxazoles 4c-f may be accounted for by considering that allylic Grignards exist as a rapidly equilibrating mixture[12] of the two forms (E) and (F) and assuming that the more abundant and less branched form (E) is the reacting species.

(E) (F)

SCHEME I



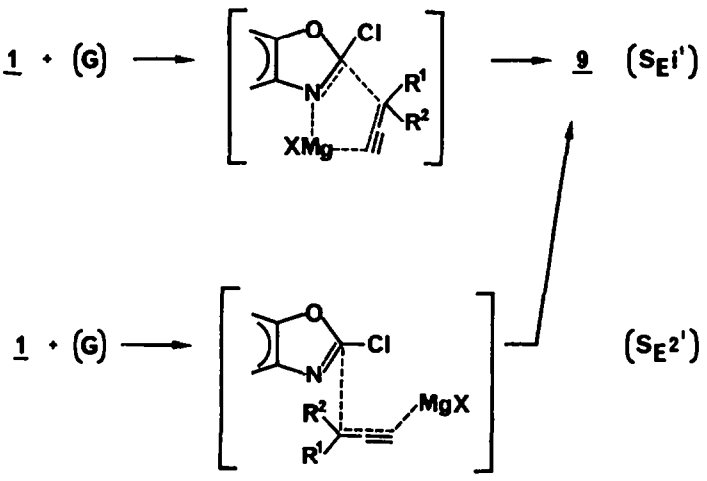
(D)

The allylic benzoxazoles 4 do not isomerize spontaneously[13] but we have found that compound 4c rapidly converts to the vinylic benzoxazole 5 upon treatment with either n-BuLi at -78°C or H_2SO_4 at reflux. Therefore, following the present procedure one may achieve either vinylic or allylic benzoxazoles which can further be elaborated to other classes of compounds. In comparison, the reaction of oxazolylalkyllithiums with carbonyls normally gives mixtures of vinylic and allylic oxazoles or suffers from retrocondensation.[14] Interestingly, the reduction of compounds 4c and 4e (H_2, Pd/C 5%) affords almost quantitative yields of the secondary and tertiary alkyl derivatives 6a and 6b respectively.

We have also found that 2-chlorobenzoxazole 1 reacts rapidly and cleanly with the Grignard reagents prepared from propargyl bromide 7a, 1-methyl-propargyl bromide 7b and 1,1-dimethylpropargyl bromide 7c giving high to excellent yields of 2-allenylbenzoxazole 8a, 2-(1-methylpropargyl) benzoxazole 9b and 2-(1,1-dimethylpropargyl) benzoxazole 9c respectively.

The formation of the acetylenic benzoxazoles 9b and 9c can yet be explained in terms of a S_Ei' or S_E2' mechanism,[15,16] involving the allenic form (G) of the Grignard reagent as the reacting species as illustrated in Scheme II. The allenic benzoxazole 8a may derive from the isomerization of the 2-propargylbenzoxazole 9a, formed as a result of the attack of the allenic form (G) ($R^1=R^2=H$) via one of the two mechanisms above. In agreement with this is the fact that the acetylenic benzoxazole 9b isomerizes to the allenic derivative 8b simply on treatment with triethylamine.

SCHEME II



The present reaction between 2-chlorobenzoxazole and unsaturated Grignard reagents allows then the preparation of potential synthetically useful 2-allyl-, 2-allenyl-, and 2-propargyl-benzoxazoles. Moreover the reduction of the branched 2-allylbenzoxazoles leads to excellent yields of the branched 2-alkylbenzoxazoles, otherwise difficult to be prepared.

Experimental Section.

^{1}H NMR spectra were recorded on either a Varian EM 360A or a Varian 390 instrument, and chemical shifts are expressed in values relative to Me_4Si as an internal standard. The infrared spectra were recorded on a Perkin-Elmer 681 spectrophotometer. Melting points were determined on a Electrothermal apparatus and are uncorrected. Flash[17] chromatographies were done with Merck 60 silica gel (230-400 mesh).

Materials. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Diethyl ether (ether) and tetrahydrofuran (THF) were distilled (twice) from sodium immediately prior to use. Petroleum ether refers to the 40-70°C boiling fraction. 2-Chlorobenzoxazole 1 was prepared from the 2-mercaptobenzoxazole and S_2Cl_2 according to the procedure reported for 2-chloro-5-methylbenzoxazole.[19] The allylic Grignard reagents derived from halides 2a-f were prepared according to the procedure reported for 1-methyl-2-propenylmagnesium bromide.[18] The Grignards derived from halides 7a-b[20] and 7c[21] were prepared as reported.

General Procedure for the Cross-Coupling of 2-Chlorobenzoxazole 1 with the Grignard Reagents obtained from the Halides 2a-f and 7a-c. The reaction of 1 with the allylmagnesium bromide is described as an example. To a stirred solution of 1 (0.3 g, 1.96 mmol) in 15 mL of CH_2Cl_2 (see Table) was added the ether solution of allylmagnesium bromide (3.9 mL, 0.77 N, 3.02 mmol) at -75°C

TABLE

Reaction of 2-chlorobenzoxazole 1 with Grignard reagents prepared from allylic 2 and propargylic halides 7.

Halide.	Reactants molar ratio	Solvent.	Temp.°C.	Product (% Yield)[c,d]	IR(CCl_4) ν cm^{-1}	^1H NMR (CCl_4) δ ppm
2a[a]	1/1.9	ether	RT	3 (35)	3620(OH) 3340(NH)	2.2(d, 6H, J =6Hz), 4.8-5.2 (m, 6H), 5.3-6.1(m, 3H), 6.2-6.9(m, 4H).
"	1/1.5	CH_2Cl_2[e]	0	3 (15) 4a (26)	1650(C=C)	3.5(d, 2H, J = 6Hz), 4.9 -5.4(m, 2H), 5.6-6.4(m, 1H), 6.8-7.7(m, 4H).
"	1/1.5	"	-50	3 (5) 4a (57)		
"	1/1.5	"	-75	3 (9) 4a (62)		
2b[a]	1/1.6	"	-30	4b (27)	1620(C=C)	1.75(s, 3H), 3.45(s, 2H) 4.75(s, 2H), 6.8-7.7(m, 4H).
"	1/1.6	"	-85	4b (100)		
2c[a]	1/1.9	"	-25	4c (97)	1645(C=C)	1.45(d, 3H, J = 7Hz), 3.6 (m, 1H), 4.8-5.3(m, 2H), 5.6-6.3(m, 1H), 6.8-7.6(m, 4H).
"	1/1.6	THF	0	4c (100)		
2d[b]	1/1.2	"	0	4d (76)	1645(C=C)	4.9(cm, 3H), 5.8-6.6(m, 1H), 6.7-7.7(m, 9H).
"	1/1.2	CH_2Cl_2[e]	0	4d (76)		
2e[b]	1/1.9	"	-30	4e (54)	1645(C=C)	1.45(s, 6H), 4.7-5.2(m, 2H), 5.6-6.3(m, 1H), 6.8 -7.6(m, 4H).
	1/1.4	THF	0	4e (100)		
2f[b]	1/1.5	"	0	4f (100)	1640(C=C)	1.4(s ,3H), 1.5(s, 6H), 1.8 (bs, 4H), 4.6-5.1(m, 3H), 5.6-6.2(m, 1H), 6.8-7.6(m, 4H).
7a[a]	1/1.5	CH_2Cl_2[e]	-78	8a (78)	1975,1945 (C=C=C)	5.2(d, 2H, J = 7Hz), 6.1(t, 3H, J = 7Hz), 6.8-7.6(m, 4H).
7b[a]	1/1.5	"	-63	9b (98)	3330(≡C-H) 2140(C≡C)	1.6(d, 3H, J = 7Hz), 2.15 (d, 1H, J = 2Hz), 3.8(qd, 1H, J = 7Hz, J = 2Hz), 6.8-7.6(m, 4H).
7c[a]	1/1.5	CH_2Cl_2/ether	-78	9c (91)	3320(≡C-H) 2130(C≡C)	1.75(s, 6H), 2.2(s, 1H), 6.8-7.7(m, 4H).

[a] Grignard reagent prepared in ether. [b] Grignard reagent prepared in THF. [c] Yields based on isolated, chromatographically pure products. [d] All new compounds are oils and gave satisfactory microanalytical data for C, H, N. [e] Reaction carried out by adding the ether (or THF) solution of the Grignard reagent to the solution of 1 in CH_2Cl_2. [f] Spectrum recorded in CCl_4/D_2O.

under nitrogen. After 30 min the reaction mixture was warmed to room temperature and quenched with a saturated NH_4Cl solution. The reaction mixture was diluted with CH_2Cl_2, separated and the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The resulting residue was flash chromatographed on silica gel, using petroleum ether-acetone 8:2 as the eluent. The first compound eluted was the 2-allylbenzoxazole 4a. The second eluted product was the N-triallylmethyl-o-aminophenol 3.

All the reactions of 2-chlorobenzoxazole 1 with the Grignard reagents derived from halides 2b-f and 7a-c were found to be clean and gave substantially one product, further purified by short flash chromatography. Data for the ring opened product 3 and for the cross-coupled products, 4a-f, 8a and 9b-c are given in the Table.

Reduction of 2-(1-methyl-2-propenyl) benzoxazole 4c and 2-(1,1-dimethyl-2-propenyl) benzoxazole 4e. 0.3 g (1.73 mmol) of 4c in 10 mL of CH_2Cl_2 and 0.15 g of 5% Pd/C were treated with H_2 (1 atm, 1.73 mmol) for 30 min. The catalyst was then removed by filtration and the dichloromethane evaporated to give 0.31 g (100%) of 2-(sec-butyl) benzoxazole 6a oil: ^1H NMR(CCl_4) δ 0.9(t, 3H, J = 7Hz), 1.3(d, 3H, J = 7Hz), 1.4-2.0(m, 2H), 2.8(q, 1H, J = 7Hz), 6.7-7.5(m, 4H).
Similary the benzoxazole derivative 4e was reduced to 2-(2-methyl-2-butyl) benzoxazole 6b oil: ^1H NMR(CCl_4) δ 0.75(t, 3H, J = 7Hz), 1.4(s, 6H), 1.7(q, 2H, J = 7Hz), 6.8-7.6(m, 4H).
Isomerization 4c → 5a. To a stirred solution of 4c (0.14 g, 0.8 mmol) in 10 mL of THF was added the n-hexane solution of n-BuLi (0.7 mL, 1.42 N, 0.99 mmol) at -78°C under nitrogen. After 20 min the reaction mixture was allowed to warm to room temperature and then quenched with sat. NH_4Cl. Extraction with ether, drying over Na_2SO_4 and removal of the solvent in vacuo gave 0.14 g (100% yield) of 2-(2-benzoxazolyl)-but-2-ene 5a: oil; ^1H NMR (CCl_4) δ 1.8(d, 3H, J = 7Hz), 2.1(s, 3H), 6.7 (m, 1H), 6.9-7.6(m, 4H).
The same conversion 4c → 5a can be carried out on refluxing 4c in ethanol, (10 mL) and 1 mL of conc. H_2SO_4.
Isomerization 9b → 8b 0.13 g of 9b was treated with a few drops of triethylamine in 15 mL of CH_2Cl_2 at room temperature. Evaporation of solvent after 30 min left quantitative yield of 2-(1-methyl-1,2-propadienyl) benzoxazole 8b: mp. 55-57°C (petroleum ether); IR (CCL_4) ν cm^{-1} 1950 (C=C=C); ^1H NMR (CCl_4) δ 2.1(t, 3H, J = 3Hz), 5.05(q, 2H, J = 3Hz), 6.7-7.5(m, 4H).

Acknowledgements: we also thank Ministero Pubblica Istruzione (Rome) for supporting this research.

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