Pergamon

Tetrahedron Letters, Vol. 38, No. 27, pp. 4845-4848, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01009-5

Unexpected Regioselectivity in the Attack of Vinyl Grignard Reagents to Bis(2-benzothiazolyl) Ketone

Carla Boga*, Luciano Forlani and Paolo E. Todesco

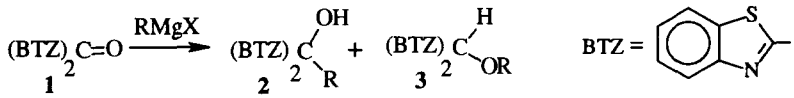
Dipartimento di Chimica Organica "A. Mangini", Università di Bologna,
Viale Risorgimento 4, 40136 Bologna, Italia.

Abstract: The addition of vinyl Grignard reagents to bis(2-benzothiazolyl) ketone affords the unexpected *O*-alkylation products in very high yields. © 1997 Elsevier Science Ltd.

During our studies on heterocyclic compounds such as thiazolyl-, benzothiazolyl- and bis(heteroaryl)methane derivatives, most of which are known as biologically active compounds, we recently investigated the reactivity of bis(2-benzothiazolyl) ketone **1**. In particular, we found that alkyl, allyl and alkynyl Grignard reagents reacted with **1** to give the corresponding carbinols **2** (Scheme 1) in quantitative yields,[1] except for phenyl magnesium halide, which did not give the expected carbinol but a mixture of unidentified products and tars, in agreement with a previous report[2] of the reaction of **1** with *p*-tolylmagnesium bromide in which the corresponding carbinol was produced with only 5% yield.

The anomalous behaviour of aryl Grignard reagents prompted us to investigate the reactivity of vinylic Grignard reagents towards **1**. Surprisingly, by using vinylmagnesium bromide we did not observe the formation of the carbinol expected by the normal 1,2-addition to carbonyl group, but we obtained quantitatively the vinyl ether **3a** derived from oxyphilic attack of the nucleophile (Scheme 1).

Scheme 1



This behaviour is unusual: very few examples of *O*-alkylation of a carbonyl group by Grignard reagents - in low to moderate yields - have been reported; typical substrates were *ortho*-quinones,[3] *ortho*-quinol acetates,[4] 9,10-phenanthraquinone[5] and benzil.[6]

Table 1 collects the results of the reactions between **1** and some vinylic Grignard reagents, carried out under different experimental conditions. The reaction was almost quantitative and total regioselectivity towards *O*-attack was observed when vinylmagnesium bromide and isopropenylmagnesium bromide were used (entries 1-4). Change of reaction temperature did not affect the regioselectivity, which, instead, was dependent on the nature of substitution pattern of the vinyl group (entry 5): the reaction with 2-methyl-1-propenylmagnesium bromide gave a mixture of carbinol **2c** and vinyl ether **3c**.

Table 1. Reactions of 1 with RMgBr[a]

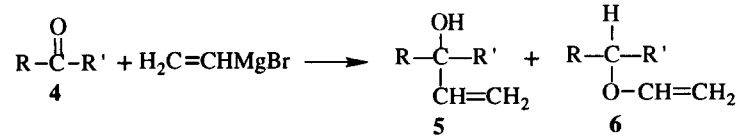
Entry	R	Molar ratio 1:RMgBr	Temp (°C)	Product 2 (yield %)	Product 3 (yield %)
1	CH_2=CH	1:1	-70	**2a** (0)	**3a** (97)[b],(92)[c]
2	CH_2=CH	1:1	0	**2a** (0)	**3a** (90)[b]
3	CH_2=CH	1:2	0	**2a** (0)	**3a** (80)[c]
4	CH_2=C(CH_3)	1:1	-70	**2b** (0)	**3b** (92)[c]
5	$(CH_3)_2$C=CH	1:1	-70	**2c** (57)[c]	**3c** (43)[c]

a) In THF for 15 min.. b) Calculated from ^{1}H NMR of crude reaction product. c) After flash chromatography.

All the products were isolated by flash chromatography and characterised,[7] but the vinyl ethers were water- and air-sensitive, and decomposed easily giving ketone **1**. In particular, deuterochloroform solutions of **3a**, after storage for many days, showed disappearance of signals of the vinyl system and appearance of strong signals of **1** together with weak signals that were ascribed to acetaldehyde. This suggests that **3a** underwent oxidation, as is known for bis(heteroaryl)methanes:[8] in this case a hemiketal was formed which in acidic media and/or in presence of water reconverted to **1** and vinyl alcohol which immediately formed the stable acetaldehyde.

In order to understand the influence of the benzothiazolyl group on this behaviour we carried the reaction of vinylmagnesium bromide with a series of ketones (Scheme 2); the results are reported in Table 2.

Scheme 2



a : R, R' = phenyl; **b** : R = 2-benzothiazolyl, R' = methyl; **c** : R, R' = 2-thiazolyl.

Table 2. Reaction of vinylmagnesium bromide with ketones[a]

Ketone	Reaction temp. (°C)	Reaction time(min)	Molar ratio ketone: RMgBr	carbinol (yield %)	vinyl ether (yield %)
4a	-70	15	1:2	**5a** (0)	**6a** (0)
4a	-70 to -40	60	1:1	**5a** (28)[b]	**6a** (0)
4a	20	120	1:1	**5a** (67)[b]	**6a** (0)
4b	-70	15	1:1	**5b** (99)[c]	**6b** (0)
4c	-70	15	1:1	**5c** (50)[c]	**6c** (50)[c]

a) Reactions performed in THF. b) Yields calculated from ^{1}H NMR spectra of crude reaction product. c) Yields calculated after flash chromatography.

Benzophenone **4a** gave only the carbinol **5a** derived from classical 1,2-addition, but the yield was appreciable only when the reaction was carried out at a higher temperature than that used with **1**, in agreement with the high reactivity of the latter with Grignard reagents.[1]

2-Benzothiazolyl methyl ketone **4b** also gave quantitatively the carbinol **5b**, whereas, using bis(2-thiazolyl) ketone **4c**, an equimolar mixture of *C*- and *O*-alkylation products was obtained.

At present it may be premature to speculate upon the mechanism of this reaction, and for this purpose work is in progress, but preliminary results suggest that not only the nature of Grignard reagent but also the presence of the N=C–C=O moiety is important. The abnormal 1,4-addition of nucleophiles, both at nitrogen in a-iminoesters[9] and at oxygen in 1,2-diketones[6] was previously observed.

In addition, the experimental data (Tables 1, 2) show that in our reactions the presence of two thiazolyl groups (together with an anellation effect) plays an important role in driving the regiochemistry of the reaction towards oxygen attack.

Typical experimental procedure.

The Grignard reagent (0.34 mmol) in THF (2 mL) was added over 5 min. to a stirred solution of **1** (0.100 g, 0.34 mmol) in THF (3 mL), cooled at -70°C. After about 15 min. the reaction mixture was quenched with saturated aqueous $(NH_4)_2SO_4$ and stirred while warming to 20°C. After extraction with Et_2O, the organic layers were washed with distilled H_2O and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Products were isolated by flash chromatography and fully characterized.[7]

Acknowledgements: The authors thank the Ministero dell'Università e della Ricerca Scientifica e Tecnologica, the Consiglio Nazionale delle Ricerche (CNR, Roma) and the University of Bologna (Progetto d'Ateneo: Biomodulatori organici: sintesi, proprietà ed applicazioni). Many thanks are due to Prof. D. Savoia for helpful discussion and to Prof. R. Boga for language revision.

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7. Selected data for new compounds, [^{13}C NMR spectra: signal multiplicities were established by DEPT experiments: CH and CH_3 as (+) and CH_2 as (-)]:
   3a: ^1H NMR (300 MHz, $CDCl_3$) δ: 8.08 (dd, 2 H, J = 8.8 Hz, J = 0.7 Hz, 4-H or 7-H), 7.89 (dd, 2 H, J = 7.9 Hz, J = 0.7 Hz, 4-H or 7-H), 7.48 (td, 2 H, 5-H or 6-H), 7.39 (td, 2 H, 5-H or 6-H), 6.75 (s, 1H, 8-H), 6.67 (dd, 1 H, J = 14.2 Hz, J = 6.8 Hz, 9-H), 4.69 (dd, 1 H, J = 14.2 Hz, J = 3.0 Hz, 10-H), 4.33 (dd, 1 H, J = 6.8 Hz, J = 3.0 Hz, 10-H); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 167.7, 152.8, 149.1(+), 135.2, 126.2(+), 125.6(+), 123.8(+), 121.8(+), 92.4(-), 78.3(+); MS (m/e): 324 (M^+), 281, 268. HRMS: $C_{17}H_{12}OS_2N_2$ requires 324.0391; found: m/e 324.0400.

3b: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.08 (d, 2 H, J = 8.5 Hz, 4-H or 7-H), 7.89 (d, 2 H, J = 7.2 Hz, 4-H or 7-H), 7.49 (td, 2 H, 5-H or 6-H), 7.43 (td, 2 H, 5-H or 6-H), 6.83 (s, 1 H, OCH), 4.24 (d, 1 H, J=3.0Hz), 4.13 (d, 1 H, J = 3.0 Hz), 2.05 (s, 3 H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$), δ: 168.3, 157.4, 152.9, 135.2, 126.1(+), 125.5(+), 123.8(+), 121.7(+), 86.7(-), 77.1(+), 20.8(+); MS (m/e): 338 (M^+), 281, 248, 191.

2c: ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.04 (δ, 2 H, J = 8.3 Hz, 4-H or 7-H), 7.86 (d, 2 H, J = 7.4 Hz, 4-H or 7-H), 7.47 (td, 2 H, 5-H or 6-H), 7.40 (td, 2 H, 5-H or 6-H), 6.32-6.30 (m, 1 H, CH=), 5.70 (s, 1 H, OH), 1.88 (d, 3 H, J = 1.5 Hz, CH_3), 1.73 (d, 3 H, J = 1.3 Hz, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$), δ : 176.4, 152.5, 143.4, 136.0, 126.5(+), 126.1(+), 125.2(+), 123.3(+), 121.8(+), 77.8, 26.9(+), 19.8(+); MS (m/e): 352(M^+), 335, 217.

3c: ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.08 (d, 2 H, J = 7.2 Hz, 4-H or 7-H), 7.91 (d, 2 H, J = 7.4Hz, 4-H or 7-H), 7.55-7.30 (m, 4 H, 5-H and 6-H), 6.47 (s, 1 H, OCH), 6.16-6.13 (m, 1 H, CH=), 1.82 (d, 3 H, J=1.3 Hz, CH_3), 1.57 (d, 3 H, J = 1.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$), δ: 168.2, 153.0, 152.0, 137.4(+), 135.4, 126.2(+), 125.5(+), 123.8(+), 121.8(+), 80.5(+), 19.4(+), 15.5(+); MS (m/e): 352 (M^+), 309, 281, 268.

5b: ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.01 (d, 1 H, J = 8.2 Hz, 4-H or 7-H), 7.87 (d, 1 H, J = 7.5 Hz, 4-H or 7-H), 7.52-7.34 (m, 2 H, 5-H and 6-H), 6.35 (dd, 1 H, J = 10.6 Hz, J = 17.2 Hz), 5.51 (d, 1 H, J = 17.2 Hz), 5.25 (d, 1 H, J = 10.6 Hz), 3.89 (s, 1 H, OH), 1.86 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$), δ: 178.7, 153.6, 142.7(+), 135.9, 126.6(+), 125.6(+), 123.5(+), 122.3(+), 114.6(-), 78.3, 29.6(+); MS (m/e): 205 (M^+), 190, 188, 162, 135.

5c: ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.77 (d, 1 H, J = 3.2 Hz), 7.34 (d, 1 H, J = 3.2 Hz), 6.62 (dd, 1 H, J = 16.9 Hz, J = 10.4 Hz), 5.60 (d, 1 H, J = 16.9 Hz), 5.56 (s, 1 H, OH), 5.34 (d, 1 H, J = 10.4 Hz); MS (m/e): 224 (M^+), 207, 112.

6c: ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.81 (d, 1 H, J = 3.3 Hz), 7.40 (d, 1 H, J = 3.2 Hz), 6.57 (dd, 1 H, J = 14.2 Hz, J = 6.8 Hz), 6.56 (s, 1 H, OCH), 4.57 (dd, 1 H, J = 14.2 Hz, J = 2.7 Hz), 4.26 (dd, 1 H, J = 6.8 Hz, J = 2.7 Hz); MS (m/e): 224 (M^+), 181, 112.

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(*Received in UK* 24 *April* 1997; *accepted* 23 *May* 1997)