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Exploration of Aberrant Behaviour of Grignard Reagents with Indole-3-carboxaldehyde: Application to the Synthesis of Turbomycin B and Vibrindole A Derivatives

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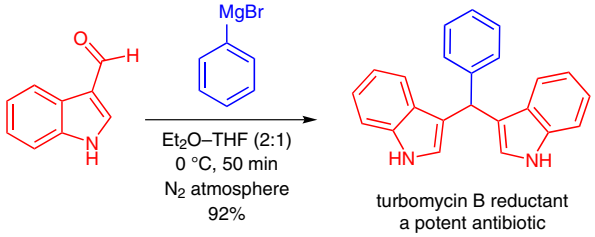

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Abstract An aberrant reaction of Grignard reagents with N-alkylated indole-3-carboxaldehyde has been observed. Contrary to the usual formation of an alcohol, it afforded an unusual bis(indolyl)methane product. A systematic study on this new mode of reactivity and its application to a synthesis of the potent antibiotic turbomycin B and vibrindole A derivatives is reported.

Key words Grignard, vibrindole, turbomycin

The reaction of Grignard reagents[1] with carbonyl compounds is frequently used in organic syntheses. Inserting magnesium metal between a carbon–halogen bond makes the carbon center nucleophilic and such reagents have special emphasis due to their umpolung reactivity.[2] Due to this, Grignard reagents have been applied in diverse organic transformations from carbonyl addition to cross-coupling reactions.[3a] Sometimes side products of this reaction can lead to unexplored chemistry. Formation of abnormal products such as pinacols,[3b,c] alkanes,[3d] and the Bartoli reaction with nitroarenes[3e,f] have been well documented with Grignard reagents. Moreover, it has been also observed that Grignard reagents can also bring about nucleophilic aromatic substitution[3g] and opening of strained ring systems.[3h] During the synthesis of some aromatic alcohols, we performed a Grignard addition (PhMgBr) to *N*-methyl indole-3-carboxaldehyde. Surprisingly, we observed a series of nonpolar reaction components instead of the expected polar alcohol on TLC analysis. After purification of the complex crude mixture, NMR spectroscopic and mass spectrometric analysis of the purified product confirmed the formation of an unusual phenyl bis(indolyl)methane (Table, entry 1).[4]

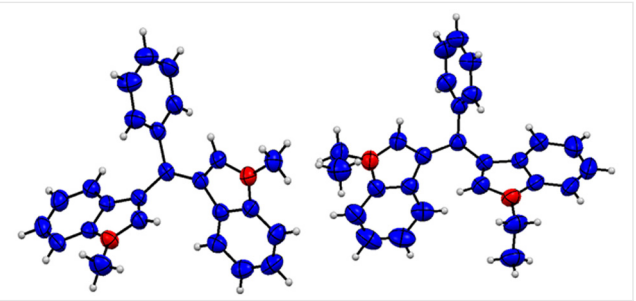
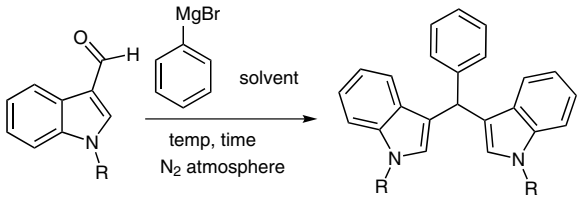


Figure 1 Crystal structures of **2aa** and **2ca**. ORTEP diagrams for the crystals showing 20% thermal ellipsoids.

The structure of the bis(indolyl)methane product was also confirmed by single-crystal X-ray analysis (Figure 1, **2aa**). This abnormal behavior of the phenyl Grignard reagent with *N*-methyl indole-3-carboxaldehyde can be partly attributed to the fact that the carbonyl group is rendered less electrophilic due to the electron-donating ability of the indole nitrogen,[5] therefore it is less reactive towards usual Grignard addition. As the yield of the bis(indolyl)methane product was low, we attempted to optimize the yield. On changing the solvent from THF to diethyl ether (Table 1, entry 2) the yield dropped to 10%, but this occurred partly because of the low solubility of *N*-methyl indole-3-carboxaldehyde. Therefore we tried this reaction in various combinations of THF and diethyl ether (Table 1, entries 3–13). The best yield (76%) was obtained with a 2:1 combination of diethyl ether and THF (Table 1, entry 5). As we presumed that the electron-donating ability of nitrogen is the key for this unusual transformation, we tested these conditions on the more electron-rich, unprotected indole-3-carboxaldehyde, and we observed a 92% yield (Table 1, entry 14). When the solvent concentration was changed from 0.5 M to 0.25 M, the yield was reduced to 84% (Table 1, entry 15) under similar conditions.

Table 1 Optimization of Reaction Conditions



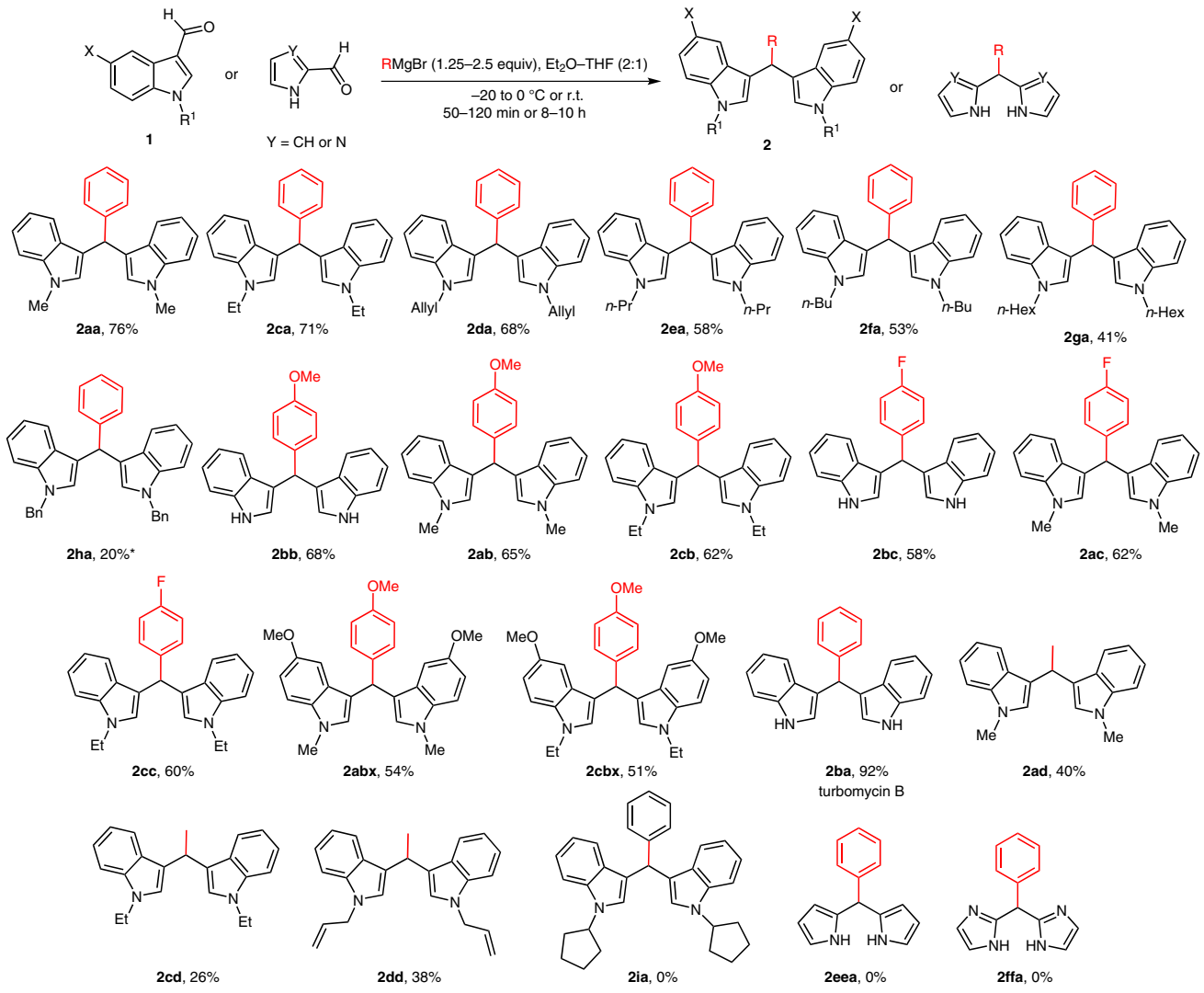
1a R = Me
1b R = H

2a R = Me
2b R = H

Entry	Aldehyde	PhMgBr (equiv)	Solvent	Solvent conc. [M]	Temp (°C)	Time (min)	Yield (%)
1	**1a**	1.25	THF	0.5	0	60	15
2	**1a**	1.25	Et_2O	0.5	0	60	10
3	**1a**	1.25	Et_2O–THF (4:1)	0.5	0	50	42
4	**1a**	1.25	Et_2O–THF (3:1)	0.5	0	50	64
5	**1a**	1.25	Et_2O–THF (2:1)	0.5	0	50	76
6	**1a**	1.25	Et_2O–THF (1:1)	0.5	0	50	64
7	**1a**	1.25	Et_2O–THF (2:1)	0.25	0	75	70
8	**1a**	1.25	Et_2O–THF (2:1)	0.1	0	90	60
9	**1a**	1.25	Et_2O–THF (2:1)	0.05	0	120	51
10	**1a**	1.25	Et_2O–THF (2:1)	0.5	–5	50	68
11	**1a**	1.25	Et_2O–THF (2:1)	0.5	–10	50	60
12	**1a**	1.25	Et_2O–THF (2:1)	0.5	–15	50	40
13	**1a**	1.25	Et_2O–THF (2:1)	0.5	r.t.	50	43
14	**1b**	2.25	Et_2O–THF (2:1)	0.5	0	50	92
15	**1b**	2.25	Et_2O–THF (2:1)	0.25	0	60	84

[a] All the reactions were carried out at a 0.5 mmol scale under N_2 atmosphere.

Intrigued by this abnormal bis(indolyl)methane formation, we explored the transformation with different N-alkylated indole-3-carboxaldehydes (Scheme 1). We protected the nitogen atom[6] of indole-3-carboxaldehyde with ethyl, allyl, *n*-propyl, butyl, hexyl, benzyl, and cyclopentyl groups, which all gave good to moderate yields (Scheme 1, **2aa**–**ha**) except *N*-benzyl (**2ha**) and *N*-cyclopentyl (**2ia**) substrates. The poor reactivity of the *N*-benzyl substrate could be caused by the presence of the relatively acidic benzylic protons, which could lead to side reactions. Furthermore, we explored this protocol with aryl Grignard reagents possessing electron-withdrawing and -donating groups. All gave the bis(indolyl)methane moiety (**2bb**–**cc**) in good yields. We also tested the reaction with electron-donating substituents on the indole ring system, which gave bis(indolyl)methane products in moderate yields (**2abx**,**cbx**). As the electron-withdrawing nitro and cyano substituents interfere with Grignard reagents, we tried the reaction of the phenyl Grignard with N-alkylated 7-azaindole 3-carboxaldehyde but no bis(indolyl)methane product was detected. Therefore we presume that the electron-rich indole system is the driving force for the reaction. To examine the reactivity of the phenyl Grignard with other nitrogenous heterocyclic aldehydes, we performed reactions with pyrrole-2-carboxaldehyde and imidazole-2-carboxaldehyde (Scheme 1, **2eea** and **2ffa**) but we could not detect any product. We also explored this protocol without protecting the nitrogen atom of indole-3-carboxaldehyde. When phenyl magnesium bromide was used as the reagent, the reaction proceeded cleanly in more than 90% yield[7] (Scheme 1, **2ba**). The product is the potent antibiotic natural product turbomycin B.[8,11] Although there are many methods[9] known for the synthesis of this natural product, this is the first report using a Grignard reagent in a single step. *N*-Methyl and *N*-ethyl indole-3-carboxaldehyde with methyl magnesium bromide gave the *N*-methyl and ethyl derivatives of the natural product vibrindole A in modest yields (Scheme 1, **2ad**,**cd**). For the synthesis of vibrindole A itself, we utilized the N-allyl precursor (Scheme 1, **2dd**). Unfortunately, deprotection of the allyl group using standard procedures[10] was not successful, due to the instability of the bis(indolyl)methane at high temperatures. Single-crystal X-ray analysis of compounds **2aa** and **2ca** (Figure 1) unambiguously confirmed the structure of the bis(indolyl)methane

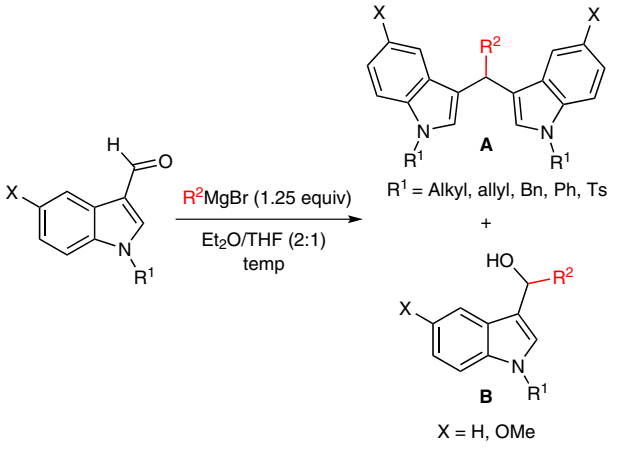


Scheme 1 Substrate scope with various Grignard reagents. [a] All the reactions were carried out at –20 °C to 0 °C or at r.t. by using 1.25 equiv of Grignard reagents with 0.5 M concentration of Et_2O–THF(2:1). [b] In the case of **2bb**, **2bc**, and **2ba**, 2.5 equiv of Grignard reagents were used. *NMR yield.

skeleton.[11] Finally, we extended our study to explore the reactivity of *N*-methyl indole-3-carboxaldehyde with various other Grignard reagents (Table 2, entries 1–6). Reactions of ethnyl, isopropyl, isopropenyl, and allyl magnesium halides (Table 2, entries 2 and 4–6) gave exclusively carbonyl addition products; on the other hand, benzyl and vinyl Grignard reagents gave the desired products in low yields along with alcohols (Table 2, entries 1 and 3). Substrates with *N*-phenyl and *N*-tosyl groups gave exclusively alcohols (Table 2, entries 11 and 12). Thus, we came to the conclusion that only aryl and methyl Grignard reagents give acceptable results (Scheme 1).

We also isolated small amounts of benzaldehyde as a side product when one equivalent of phenyl Grignard reagent was used. To investigate the mechanism, we performed the reaction with 4-methoxy- and 4-fluorophenyl Grignard reagents and, as expected, we isolated the corresponding 4-methoxybenzaldehyde and 4-fluorobenzaldehyde. From this observation, we suggest a plausible mechanism as described in Scheme 2. We propose that the initial Grignard addition product undergoes fragmentation by expulsion of $XMgO^-$ to form a conjugated iminium species **3** (due to the electron-rich nature of the indole ring at C-3) and further fragmentation leads to the formation of transient indole magnesium reagent **4** and the corresponding aldehyde. Reaction between the two intermediates **3** and **4**

Table 2 Reaction of Various Grignard Reagents with Differently Substituted Indole 3-Carboxaldehyde under Optimized Temperature

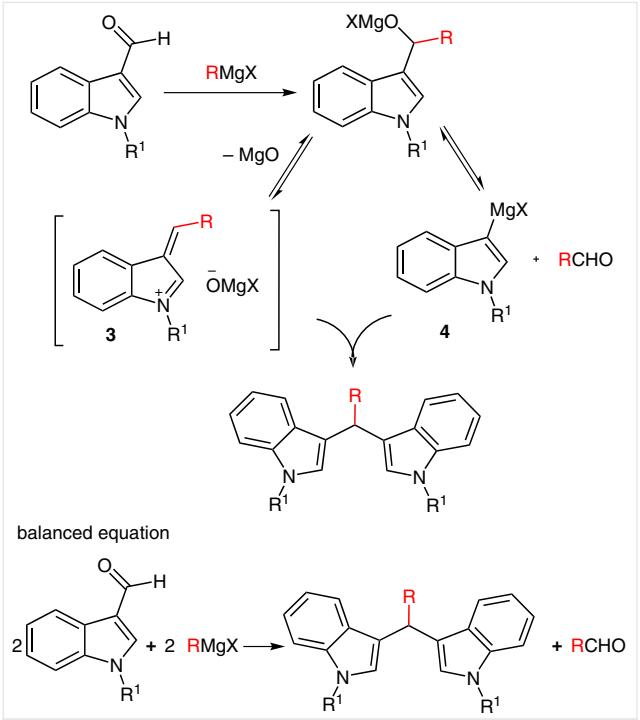


Entry	R^1	R^2	Temp (°C)	Product A (%)	Product B (%)
1	Me	Bn	–20	20	70
2	Me	ethynyl	0	0	99
3	Me	vinyl	–10	16	60
4	Me	isopropyl	–10	0	80
5	Me	isopropenyl	–10	0	99
6	Me	allyl	–10	0	90
7	Et	Et	–10	0	70
8	Et	allyl	–20	15	30
9	Bn	Me	–10	0	80
10	Bn	allyl	–20	10	50
11	Ph	Ph	0	0	99
12	Ts	Ph	0	0	99

[a] All the reaction were carried out at 0.5 mmol scale under N_2 atmosphere.

leads to the formation of the bis(indolyl)methane. This mechanism also explains the reason why indole 3-carboxaldehydes possessing electron-withdrawing substituents do not lead to bis(indolyl)methane products. To support the mechanism and observation of aldehyde we added an excess of phenyl Grignard to the above reaction and confirmed the formation of diphenylmethanol.

In conclusion we have developed a new nucleophilic addition reaction of methyl and aryl Grignard reagents with indole-3-carboxaldehyde. Although literature reports[12,13] have disclosed how to synthesize bis(indolyl)methanes, to the best of our knowledge this strategy is the first report[14] using indole-3-carboxaldehyde and a Grignard reagent.[15]



Scheme 2 Proposed mechanism

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588885.

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(7) PhMgBr in Et_2O (3 M) was used. It was observed that, when the same reaction was carried out using THF alone as a solvent, the alcohol was formed as exclusive product in the same reaction time instead of the bisindolylmethane.

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(14) Based on Scifinder search till 14 April 2016.

(15) **Procedure for the Synthesis of Representative Substrate Turbomycin B Reductant {3-[(1*H*-indol-3-yl)(phenyl)methyl]-1*H*-indole}**

Indole-3-carboxaldehyde was dissolved in a Et_2O–THF (2:1) mixture and the solution cooled to 0 °C. The Grignard reagent (PhMgBr, 2.5 equiv) was added dropwise to the solution. After addition, the reaction mixture was stirred at the same temperature for 50 min. After completion of the reaction (monitored by TLC), sat. aq NH_4Cl was added to quench the reaction, and the reaction mixture was allowed to warm to r.t. The resultant mixture was then extracted with EtOAc or CH_2Cl_2 (3×) and dried over anhydrous Na_2SO_4. The resultant solution was filtered and concentrated under vacuum to obtain the crude product, which was then purified by column chromatography using a hexane–EtOAc solvent system to give turbomycin B.

Note: If the above-mentioned reaction was performed in just THF, exclusively the alcohol product was formed in the given time. It was observed that the crude mixture must be purified within 1 h of completion of the reaction, and the concentration of the reaction mixture must be carried out at moderate temperatures (30–35 °C) under vacuum. CH_2Cl_2 (a low boiling solvent) was preferred over EtOAc for extraction purposes.

White solid; mp 125–127 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (s, 2 H) 7.30 (d, 2 H, *J* = 8.2 Hz), 7.27–7.24 (m, 4 H), 7.20–7.16 (m, 2 H), 7.14–7.06 (m, 3 H), 6.92 (t, 2 H, *J* = 6.9 Hz), 6.54 (d, 2 H, *J* = 2.1 Hz), 5.80 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.9, 136.6, 128.7, 128.2, 127.0, 126.1, 123.6, 121.9, 120.0, 119.7, 119.2, 111.0, 40.1.