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REMARKABLY EASY OXIDATION OF ALKYLZINC REAGENTS IN THEIR REACTIONS WITH ELECTROPHILES TO PRODUCE ALKOXYLATED INSTEAD OF THE EXPECTED ALKYLATED PRODUCTS

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Abstract-Alkylzinc reagents, in contrast to arylzinc reagents, react with two series of α-benzotriazolylalkylamines to give oxidized products formed by the incorporation of an atom of oxygen into the carbon-zinc bond even when the reactions are carried out under argon. Thus, benzotriazole derivatives of 4,5-disubstituted imidazolidinone (**2**) and *N*-Boc-2-benzotriazolylpyrrolidine (**7**) gave oxidized products (**4a-b**) and (**8a-c**), respectively. The abnormal reaction course was traced to molecular oxygen dissolved in the THF. The expected, unoxidized products (**9a-d**) were obtained under rigorous argon purge of the THF solvent and solutions.

Due to their easy and high yield preparations, their functional group tolerance and high product yields, as well as the significant stereoselectivity of their reactions, organozinc reagents have been widely used in organic synthesis. [1] For example, recent studies have been devoted to the preparation of chiral alcohols by the asymmetric addition of diethylzinc to aldehydes in the presence of various enantioselective catalysts. [2] Organozinc reagents are particularly useful in substitution reactions of benzotriazole derivatives, especially those of type (**1**), representing masked oxoniums, thioniums or iminium salts, as documented by mutiple examples (Figure 1). [3] Although organozinc reagents are significantly less nucleophilic than Grignard reagents, they are more reactive toward benzotriazole compounds of type (**1**) due to coordination of the zinc atom at the N3 of the benzotriazole ring which enhances the leaving group ability

of the benzotriazole group. Moreover, highly basic Grignard and organolithium reagents can cause deprotonation at the carbon adjacent to the benzotriazole moiety which is much reduced when organozinc reagents are applied.

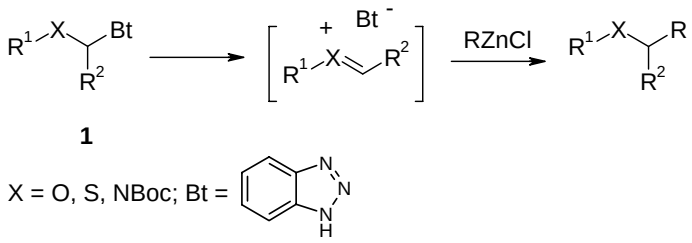

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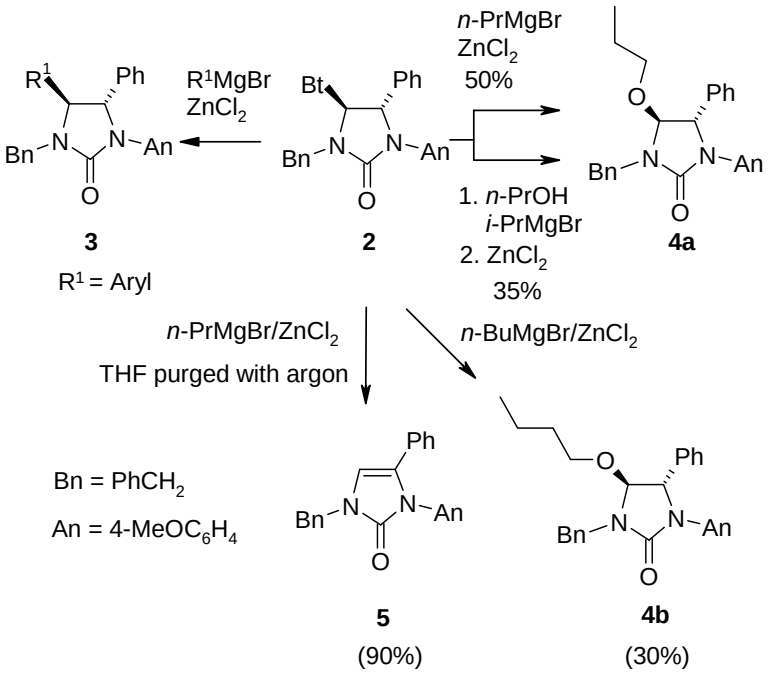
Figure 1

The sensitivity of organometallic reagents in general, and of organozinc reagents in particular, to air oxidation is well known. [1] Such reactions have been previously used to prepare alcohols, [4a] hydroperoxides [4a-c] and epoxides (using dialkylzinc compounds). [4d-f] However, in all these published procedures, to achieve the oxygen insertion, the solution of the organometallic reagent was purged with oxygen or exposed to the air; e.g. for the conversion of di(1-octyl)zinc into 1-octanol, oxygen was bubbled at 0 ^{o}C for 1 h. [4a] We now report surprising and apparently novel facile oxidations of alkylzinc reagents leading to alkoxy products in good to excellent yields instead of the expected alkyl derivatives.

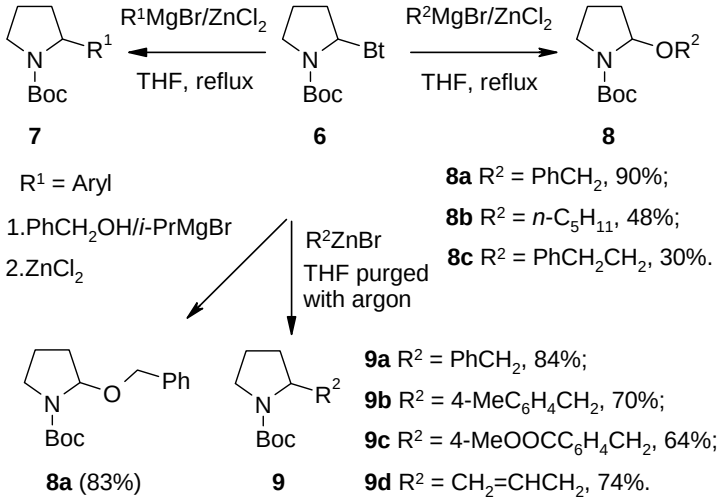


Scheme 1

We demonstrated earlier that arylzinc reagents successfully replaced the benzotriazole moiety in *trans*-4-phenyl-5-benzotriazolylimidazolidinone (**2**) affording the expected products (**3**) (Scheme 1). [5a] We now show that, under the same reaction conditions as those previously used for arylzinc reagents, alkylzinc

reagents give oxygen insertion products. Thus, **2** reacted with *n*-PrZnCl (generated *in situ* from *n*-PrMgBr and $ZnCl_2$) under an argon atmosphere in refluxing THF (no reaction occurred at 20 ^oC) to give **4a** (50%) together with elimination product (**5**) (30%). The structure of **4a** was supported by NMR spectra and HRMS; the H4/H5 coupling constant of 1.1 Hz indicated the *trans* geometry for **4a**. [5a,6] The structure of **4a** was additionally confirmed by its synthesis in 35% yield from **2** and *n*-PrOZnCl (generated *in situ* from *n*-PrOMgBr and $ZnCl_2$) at reflux in THF. The analogous oxygen insertion compound (**4b**) was obtained in 30% yield from **2** when *n*-BuZnCl was used as a nucleophile.

We reported earlier that treatment of *N*-Boc-2-benzotriazolylpyrrolidine (**6**) with arylzinc reagents as nucleophiles afforded the expected 2-arylpyrrolidines (**7**) (Scheme 2). [5b] However, under conditions identical to those used for arylzinc halides, including conducting the reactions under an argon atmosphere, three different alkylzinc reagents once again produced only oxidation products (**8a-c**) in variable yields: the results are summarized in Scheme 2. The structures (**8a-c**) were all supported by NMR spectra and CHN analysis (or HRMS). Furthermore, the structure of **8a** was confirmed by its identity with the authentic **8a** synthesized from **6** and $PhCH_2OZnCl$ (generated *in situ* from $PhCH_2OMgBr$ and $ZnCl_2$).



Scheme 2

To avoid such oxidation, the presence of oxygen must be meticulously excluded. To achieve this, the reaction system was vacuumed at 25 ^oC using oil pump for about 30 min, then filled with argon. Argon was also bubbled through the THF solution prior to and throughout the whole reaction. Under these conditions, treatment of **2** with *n*-PrZnCl (generated *in situ* from *n*-PrMgBr and $ZnCl_2$) gave only the elimination product (**5**) (90% yield) and no oxidation product was observed (Scheme 1). This illustrated that oxygen in the reaction system indeed influences the reaction and *n*-PrZnCl (in contrast to arylzinc

reagents) in this case is insufficiently nucleophilic (and/or too basic) to afford the desired substitution product of type (**3**). However, under similar conditions, reaction of **7** with generated *in situ* $PhCH_2ZnCl$ (obtained from $PhCH_2MgBr$ and $ZnCl_2$) gave the desired compound (**9a**) in 84% yield (Scheme 2). Although **9a** has the same R_f value as the corresponding oxidation product (**8a**) (silica TLC plates / (MeCOOEt : Hexanes = 1 : 5)), the spectra of compounds (**8a**) and (**9a**) are different. Thus, H2 appears as two broad singlet peaks in the ^1H NMR spectra of **9a** at 3.94 and 4.03 ppm, and C2 appears in the ^{13}C NMR spectra at 58.8 ppm. For **8a**, H2 signals were shown as two broad singlets at 5.30 and 5.42 ppm, and C2 appeared at 87.6 ppm. When $4\text{-}MeC_6H_4CH_2ZnCl$ and $4\text{-}MeOOCC_6H_4CH_2ZnCl$ were used as nucleophiles, the corresponding desired product (**9b**) [7] and (**9c**) was also obtained, respectively. When allylzinc bromide was used as a nucleophile, the corresponding desired product (**9d**) was obtained in 74% yield from **2**.

The alkoxy compounds mentioned above evidently arise from ROZnBr intermediates formed from RZnBr and O_2. Alkyl zinc reagents appear to be much more sensitive to oxygen than aryl zinc reagents; such a difference in reactivity also applies to the isolated compounds. [8]

The work presently described appears to possess two novel aspects: (i) the oxidation of alkylzinc reagents by very small amounts of oxygen dissolved in a solvent, [9] and (ii) the isolation in preparatively useful yields of products with C-alkoxy groups (the nearest analogy to which appears to the isolation of 2-allylperoxy-1,2-dihydroquinolines [4b]).

In conclusion, we have discovered that easy oxidation of alkylzinc reagents in their reactions with benzotriazole derivatives can lead to C-alkoxy products in preparatively useful yields although the use of arylzinc reagents under similar reaction conditions gives the corresponding C-aryl products.

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EXPERIMENTAL

General Comments. Melting points were determined on a hot stage apparatus and are uncorrected. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $CDCl_3$ with TMS as the internal reference. THF was distilled from sodium/benzophenone. All reactions were carried out under argon atmosphere. Compounds (**2**) and (**6**) were prepared according to the literature. [5]

General Procedure for the Synthesis of Compounds (4a-b, 5, and 8a-c). To a solution of $ZnCl_2$ (2.5 mmol, 2.5 mL 1.0 M in Et_2O) in THF (10 mL), Grignard reagent RMgBr (2.5 mmol) was added at 0 ^oC. Then the solution was warmed up to rt and stirred further for about 20 min. Compound (**2**) or (**6**) (0.5 mmol) in THF (10 mL) was added to this organozinc reagent, and the reaction mixture was heated under reflux for 12 h. The solution obtained was cooled down to rt and 5 % ammonium hydroxide aqueous solution was added. Then the organic layer was separated and the aqueous solution was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, the solvents were evaporated *in vacuo* and the residue was subjected to silica gel chromatography (MeCOOEt/Hexanes = 1/3) to give products (**4a-b, 5** and **8a-c**), respectively.

***trans*-1-Benzyl-3-(4-methoxyphenyl)-4-phenyl-5-propoxytetrahydro-2*H*-imidazol-2-one (4a):** yellow oil. Yield 50%. ^1H NMR δ 0.94 (t, *J* = 7.4 Hz, 3H), 1.55–1.62 (m, 2H), 3.30–3.33 (m, 1H), 3.43–3.48 (m, 1H), 3.72 (s, 3H), 4.19 (d, *J* = 15.1 Hz, 1H), 4.46 (d, *J* = 1.1 Hz, 1H), 4.88 (d, *J* = 1.1 Hz, 1H), 4.94 (d, *J* = 15.1 Hz, 1H), 6.77 (d, *J* = 9.1 Hz, 2H), 7.19–7.32 (m, 10H), 7.37 (d, *J* = 9.1 Hz, 2H); ^{13}C NMR δ 10.7, 23.0, 44.6, 55.4, 65.0, 67.8, 90.1, 114.0, 121.3, 125.9, 127.4, 128.0, 128.2, 128.5, 129.1, 132.0, 136.9, 138.6, 155.5, 156.8. HRMS Calcd for $C_{26}H_{29}N_2O_3$: 417.2178 (M+1). Found: 417.2178 (M+1).

***trans*-1-Benzyl-5-butoxy-3-(4-methoxyphenyl)-4-phenyltetrahydro-2*H*-imidazol-2-one (4b):** yellow oil. Yield 30%. ^1H NMR δ 0.92 (t, *J* = 7.2 Hz, 3H), 1.34–1.42 (m, 2H), 1.45–1.57 (m, 2H), 3.34–3.39 (m, 1H), 3.46–3.52 (m, 1H), 3.73 (s, 3H), 4.19 (d, *J* = 15.1 Hz, 1H), 4.46 (d, *J* = 1.2 Hz, 1H), 4.88 (d, *J* = 1.2 Hz, 1H), 4.96 (d, *J* = 15.1 Hz, 1H), 6.77 (d, *J* = 9.1 Hz, 2H), 7.18–7.32 (m, 10H), 7.37 (d, *J* = 9.1 Hz, 2H); ^{13}C NMR δ 13.9, 19.3, 31.8, 44.6, 55.4, 65.1, 65.9, 90.1, 114.0, 121.3, 125.9, 127.4, 128.0, 128.2, 128.5, 129.1, 132.1, 136.9, 138.6, 155.5, 156.8. HRMS Calcd for $C_{27}H_{31}N_2O_3$: 431.2335 (M+1). Found: 431.2348 (M+1).

1-Benzyl-3-(4-methoxyphenyl)-4-phenyl-1,3-dihydro-2*H*-imidazol-2-one (5): white needles, mp 95–96 ^oC (from hexanes and methylene chloride). [5a] ^1H NMR δ 3.79 (s, 3H), 4.90 (s, 2H), 6.32 (s, 1H), 6.86 (d, *J* = 8.9 Hz, 2H), 6.99–7.02 (m, 2H), 7.13–7.17 (m, 5H), 7.34–7.38 (m, 5H); ^{13}C NMR δ 47.3, 55.4, 108.8, 114.2, 124.2, 126.9, 127.2, 127.9, 128.2, 128.3, 128.4, 128.8, 129.4, 136.7, 153.4, 158.4.

***tert*-Butyl 2-Benzyloxy-1-pyrrolidinecarboxylate (8a):** yellow oil. Yield 90%. ^1H NMR δ 1.48 and 1.51 (2 s, 9H), 1.68–2.10 (m, 4H), 3.27–3.47 (m, 2H), 4.50–4.69 (m, 2H), 5.30 and 5.42 (2 br s, 1H), 7.15-

7.32 (m, 5H); ^{13}C NMR δ 22.7 (21.7), 28.4 (28.6), 33.0 (32.5), 45.9 (45.4), 69.9 (70.2), 79.6 (80.0), 87.5 (87.6), 127.2 (126.9), 127.4, 128.2 (128.4), 139.1 (138.6), 154.2 (155.2). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.60; H, 8.43; N, 5.20.

***tert*-Butyl 2-Pentyloxy-1-pyrrolidinecarboxylate (8b):** yellow oil. Yield 48%. ^{1}H NMR δ 0.77–0.92 (m, 3H), 1.27–1.35 (m, 4H), 1.48 (s, 9H), 1.52–1.59 (m, 2H), 1.75–2.05 (m, 4H), 3.28–3.52 (m, 4H), 5.12 and 5.24 (2 br s, 1H); ^{13}C NMR δ 14.0, 21.8, 22.5, 22.7, 28.4, 29.6, 32.9 (32.3), 45.9 (45.3), 67.9 (68.3), 79.8 (79.5), 87.3, 154.4 (155.2). Anal. Calcd for $C_{14}H_{27}NO_3$: C, 65.33; H, 10.57; N, 5.44. Found: C, 65.44; H, 10.92; N, 5.55.

***tert*-Butyl 2-Phenethyloxy-1-pyrrolidinecarboxylate (8c):** yellow oil. Yield 30%. ^{1}H NMR δ 1.45 (s, 9H), 1.72–2.03 (m, 4H), 2.86 (t, *J* = 7.1 Hz, 2H), 3.32–3.40 (m, 2H), 3.76–3.82 (m, 2H), 5.14 and 5.29 (2 br s, 1H), 7.20–7.27 (m, 5H); ^{13}C NMR δ 21.7 (22.7), 28.4, 32.3 (32.9), 36.4, 45.8 (45.3), 68.6 (68.8), 79.5 (79.8), 87.2 (87.4), 125.9, 128.1, 128.7 (128.9), 139.1 (139.2), 154.2 (155.1). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.76; H, 8.99; N, 4.50.

Synthesis of *tert*-Butyl 2-Benzyl-1-pyrrolidinecarboxylate (9a): The 100 mL round-bottom flask was vacuumed for around 30 min using oil pump, then filled with argon. The solution of $ZnCl_2$ (2.5 mmol, 2.5 mL 1.0 M in Et_2O) was added to THF (10 mL) in the above flask. After argon was bubbled through the solution for 15 min, $PhCH_2MgBr$ (2.5 mL, 2.5 mmol, 1.0 M in THF) was added at 0 ^{o}C, then the solution was warmed up to room temperature and stirred further for about 20 min under continuous bubbling argon through the solution. Compound (**6**) (144mg, 0.5 mmol) in THF (10 mL) was added to the above prepared solution of organozinc reagent, then the mixed solution was further purged with argon for 15 min at rt. Next the reaction solution was heated under reflux for 12 h under argon atmosphere. The solution was cooled down to rt and 5% ammonium hydroxide aqueous solution was added. Then the organic layer was separated and the aqueous solution was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, the solvents were evaporated *in vacuo* and the residue was subjected to silica gel chromatography (MeCOOEt/Hexanes = 1/5) to give **9a**[10] as yellow oil in 84% yield. ^{1}H NMR δ 1.51 (s, 9H), 1.62–1.75 (m, 4H), 2.48-2.55 (m, 1H), 3.03–3.18 (m, 1H), 3.28 (br s, 1H), 3.36 (br s, 1H), 3.94 and 4.03 (2 br s, 1H), 7.18–7.29 (m, 5H); ^{13}C NMR δ 22.6 (23.4), 28.6, 29.6 (28.8), 40.5 (39.5), 46.3 (46.8), 58.8, 79.2 (79.0), 126.2, 128.4, 129.4 (129.5), 139.2, 154.5.

General Procedure for the Synthesis of Compounds (9b-d). The 100 mL round-bottom flask containing activated zinc powder (4.5 mmol, 293 mg) was vacuumed for around 30 min using oil pump, then filled with argon. Then THF (10 mL) was added into the above flask. After argon was bubbled through THF solution for 15 min, RBr (3 mmol) in THF (10 mL) was added at rt and the reaction mixture was stirred for about 15 min under continuous bubbling argon through the solution. Then the above solution was heated under reflux for 10 h under argon and cooled down to rt. The solution was decanted and transferred to another 100 mL round-bottom flask which had been vacuumed and filled with argon. Compound (**6**) (144 g, 0.5 mmol) in THF (10 mL) was added to the above clear solution of organozinc reagent, then the mixed solution was further purged with argon for 15 min rt. Next the reaction solution was heated under reflux for 12 h under argon atmosphere. The solution was cooled down to rt and 5% ammonium hydroxide aqueous solution was added. Then the organic layer was separated and the aqueous solution was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, the solvents were evaporated *in vacuo* and the residue was subjected to silica gel chromatography (MeCOOEt/Hexanes = 1/5) to give **9b-d**, respectively.

***tert*-Butyl 2-(4-Methylbenzyl)-1-pyrrolidinecarboxylate (9b):** yellow oil. Yield 70%. ^{1}H NMR δ 1.72 (s, 9H), 1.90–1.98 (m, 4H), 2.53 (s, 3H), 2.65–2.72 (m, 1H), 3.20–3.36 (m, 1H), 3.49 (br s, 1H), 3.57 (br s, 1H)), 4.12 and 4.21 (2 br s, 1H), 7.25–7.47 (m, 4H); ^{13}C NMR δ 21.0, 22.6 (23.4), 28.6, 29.5, 40.1 (39.1), 46.3 (46.8), 58.9, 79.2 (79.0), 129.0, 129.2, 129.4, 136.0, 154.5. Anal. Calcd for $C_{17}H_{25}NO_2$: N, 5.09. Found: N, 5.28.

***tert*-Butyl 2-[4-(Methoxycarbonyl)benzyl]-1-pyrrolidinecarboxylate (9c):** yellow oil. Yield 64%. ^{1}H NMR δ 1.51 (s, 9H), 1.67–1.77 (m, 4H), 2.61–2.67 (m, 1H), 3.08–3.36 (m, 3H), 3.91 (s, 3H), 3.96 and 4.05 (2 br s, 1H), 7.22–7.29 (m, 2H), 7.96 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR δ 22.6 (23.4), 28.6, 29.7 (28.9), 40.7 (39.6), 46.3 (46.8), 52.0, 58.5, 79.4 (79.2), 129.4, 129.6, 129.8, 144.7, 154.5, 167.1. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.28; H, 8.20; N, 4.61.

***tert*-Butyl 2-Allyl-1-pyrrolidinecarboxylate (9d):** [9] yellow oil. Yield 74%. ^{1}H NMR δ 1.40 (s, 9H), 1.46–1.80 (m, 4H), 2.02–2.09 (m, 1H), 2.34–2.46 (m, 1H), 3.24 (br s, 2H), 3.69 and 3.77 (2 br s, 1H), 4.95–5.01 (m, 2H), 5.64–5.72 (m, 1H); ^{13}C NMR δ 22.9 (23.6), 28.5 (28.4), 29.7 (30.1), 39.0 (38.2), 46.3 (46.7), 56.7, 79.0, 117.0, 135.3, 154.5.

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