Unexpected reactions of organozinc reagents with *N*-acylbenzotriazoles

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This manuscript is dedicated to Prof. B. S. Thyagarajan

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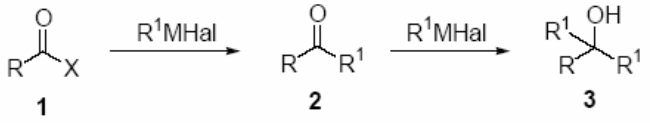
Abstract

Coupling *N*-acylbenzotriazoles with aliphatic and benzylic organozinc reagents in the presence of zinc bromide / Pd(II) catalyst (or zinc bromide / Ni(0) catalyst) did not result in formation of the expected ketones, but instead gave the corresponding carboxylic acid esters. This reaction apparently occurs by the insertion of oxygen dissolved in the solvent into the organozinc compound.

Keywords: *N*-Acylbenzotriazoles, organozinc reagents, oxygen insertion

Introduction

The transformation of carboxylic acid derivatives **1** into the corresponding ketones **2** (Scheme 1), avoiding over-reaction to tertiary alcohols **3**, is important and much studied. Acyl chlorides, esters and amides have all been utilized. Selective conversions of acyl chlorides into the corresponding ketones have been studied with a wide variety of organometallics, including Grignards (Fe^{3+} catalysis),[1] organoboron (Pd^0 catalysis),[2] organonickel,[3] organozinc (Pd^{2+} catalysis),[4] organotin (Pd catalysis),[5] and organomercury (Pd^0 catalysis)[6] reagents (a comprehensive review on such reactions has recently been published[7]).



Scheme 1

The high reactivity of acyl halides and their incompatibility with acid-sensitive functionalities have driven efforts to find alternative solutions, with the major emphasis on amides. *N*,*N*-Dialkylamides with alkyl-, aryl-[8] or vinyl-[9] lithium and Grignard[10] reagents afford

ketones in good yields. Various non-aromatic *N*-acylheterocycles, such as *N*-acyl-aziridines,[11] -pyrrolidines, -isoxazolines, and –isoxazines,[12] react cleanly with alkyl- and alkynyl-lithiums providing the corresponding ketones.

N-Acylimidazoles are converted into ketones by treatment with organolithium or organosodium derivatives of nitro compounds, sulfones, esters, etc.[13] Recently, nucleophilic substitution of an imidazolyl group with a 1-lithioalkene was used successfully for the stereoselective synthesis of α,β-unsaturated ketones.[14] Cleavage with Grignard reagents in solution in the absence of any catalyst is reported only for α-keto-substituted substrates.[15] *N*-Aroylimidazoles give with Grignards almost exclusively tertiary alcohols **3** even at low temperatures.[16] However, in the reactions of *N*-acylimidazoles with Grignard reagents two approaches could be used to prevent a significant formation of tertiary alcohols: i) using certain additives, such as equimolar amounts of TMSOTf or boron trifluoride etherate[17] or catalytic amount (10 mol%) of $FeCl_3$;[18] or ii) hindering access of the Grignard reagent to the carbonyl group by applying resin-bound acylimidazoles.[19] Reactions of 1-acyl-3,5-dimethylpyrazoles with Grignards usually afford mixtures of the corresponding ketones and tertiary alcohols,[20] although the cleavage with Reformatsky reagents leads only to the ketone formation.[21]

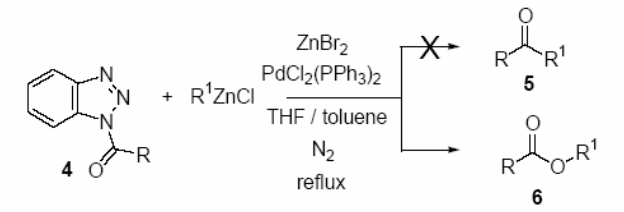
Nucleophilic substitution using other organometallics can sometimes be advantageous for performing the clean and high-yielding transformations of this type. Thus, *N*-acylimidazoles react with organotitanium compounds to afford the corresponding ketones in high yield,[16] as do *N*-acyl-imidazoles, -benzimidazoles and -benzotriazoles with organoaluminium compounds.[22] However, indium mediated coupling of allylic bromides with acylimidazoles provides mixtures of ketones and tertiary alcohols in ratios depending on the substrate structures.[23]

N-Acylbenzotriazoles are advantageous carboxylic acid derivatives in that they are stable and easily prepared in one step from the carboxylic acids even in cases where an acid-sensitive functionality is present.[25] Their reactivity is significantly enhanced by Lewis acids (especially, Zn^{2+} salts), and that makes them convertible by less active organometallic reagents. Viewing these compounds as potentially useful intermediates for transformations of carboxylic acids into ketones, we attempted the reaction of readily available *N*-acylbenzotriazoles with a number of organozinc reagents in the presence of a Lewis acid and a Pd^{2+} or Ni catalyst.

Results and Discussion

The starting *N*-acylbenzotriazoles **4a-i** (Table 1) were easily prepared by acylation of benzotriazole with acyl chlorides in the presence of a base (method A)[24] or, for acid-sensitive substrates, by the reaction of the corresponding carboxylic acid with readily available 1-benzenesulfonylbenzotriazole (method B).[25] *N*-Acylbenzotriazoles were unaffected by heating with Grignard reagents or organozinc reagents in the presence of an equivalent of anhydrous zinc bromide (the starting materials were recovered). Neither was reaction observed in the presence of a catalytic amount of bis(triphenylphosphino)palladium(II) dichloride. However, the simultaneous presence of zinc bromide and the palladium(II) catalyst promoted the complete conversion of the starting *N*-acylbenzotriazoles into single products in a rate depending on a type of the Grignard reagent used. To our surprise, the products formed were not the expected ketones

5, but the corresponding esters **6a-i** (Scheme 2, Table 2). The structures of the products were assigned by comparison of their ^{1}H and ^{13}C NMR data with those published in literature, by GC/MS analysis (for **6d**) and by independent preparation of *n*-propyl 2-furoate **6e** following the known literature procedure.[26] The analogous formation of esters instead of ketones was previously reported as a concurrent reaction occurring on interaction of *N*-acylimidazoles with Grignard reagents at elevated temperatures.[17b] Recently, in our group the very great ease of the oxidation of alkylzinc reagents, in contrast to their arylzinc counterparts, during the reactions with benzotriazolyl-substituted imidazolidinones and pyrrolidines has been demonstrated.[27]



Scheme 2

Table 1. Preparation of *N*-acylbenzotriazoles **4**

Compd.	R	Method	Mp, °C	Lit. mp, °C	Yield, %
4a	CH_3	A	50−51	51−52[24]	90
4b	CF_3	A	86−89	89−91[28]	65
4c	*t*-Bu	A	70−72	72−73[24]	95
4d	Ph	A	109−111	112−113[24]	56
4e	4-$MeOC_6H_4$	A	108−109	108−109[24]	72
4f	2-furyl	B	165−166	165−166[24]	70
4g	3-furyl	B	91-92	−	86
4h	2-thienyl	B	172−173	−	89
4i	3-pyridyl	B	90−92	86−89[24]	70

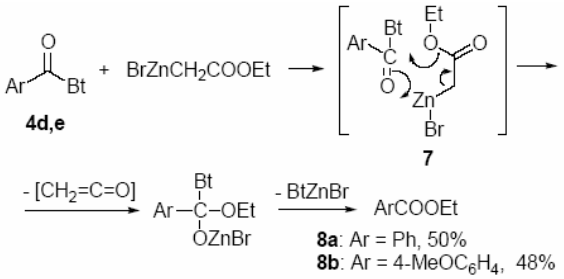
Table 2. Preparation of esters **6**

Entry	Compd.	R	R^1	X	Catalyst	Reaction time, h	Yield, %
1	**6a**	Me	$PhCH_2$	Br	Pd(II)	16	58
2	**6b**	Ph	$PhCH_2$	Br	Pd(II)	16	70
3	**6b**	Ph	$PhCH_2$	Br	Ni(0)	16	81
4	**6c**	4-$MeOC^6H_4$	$PhCH_2$	Br	Pd(II)	16	62
5	**6d**	2-furyl	$PhCH_2$	Br	Pd(II)	16	67
6	**6e**	2-furyl	*n*-Pr	I	Pd(II)	50	55
7	**6f**	2-furyl	*i*-Pr	I	Pd(II)	50	53
9	**6g**	2-thienyl	$PhCH_2$	Br	Ni(0)	12	81
10	**6h**	3-furyl	$PhCH_2$	Br	Ni(0)	12	52
11	**6i**	3-furyl	*n*-Pr	I	Ni(0)	16	44

All the reactions described in the present paper have been carried out under nitrogen atmosphere, the formation of these oxygen insertion products could be ascribed to the presence of molecular oxygen either in the nitrogen flow or in a solvent. To find out the source of oxygen and exclude it, first we carried out the reaction of 1-benzoylbenzotriazole **4d** with benzylzinc chloride under argon protection (other reaction conditions being the same as previously applied). However, the outcome of this reaction did not change: only the corresponding ester **6b** was obtained. Deoxygenating the solvent (a mixture of THF and toluene) was achieved by bubbling dry argon through the reaction mixture for 30 min prior heating and throughout the course of the reaction. Under these conditions, the formation of the ester **6b** was greatly suppressed (full conversion of the starting 1-benzoylbenzotriazole **4d** required a prolonged reaction time and the yield of **6b** was significantly lower); however, the ester **6b** was still obtained as the main product, while only traces of the corresponding ketone were observed in the ^{1}H NMR spectrum of the reaction mixture.

We have found that the rate of ester formation and the product yields also depend markedly on the nature of the R and R^1 substituents. Thus, reactions with aliphatic organozinc reagents requires 40-50 h of refluxing in THF/toluene under nitrogen while the analogous reactions with more active benzylzinc bromide were complete in 14-16 h (Table 2). Attempts to displace the benzotriazole moiety in *N*-trifluoroacetylbenzotriazole **4b** and *N*-*t*-butylcarbonylbenzotriazole **4c** by benzylzinc bromide, or in *N*-(3-pyridylcarbonyl)benzotriazole **4i** with PhZnBr or *n*-BuZnBr, failed under these conditions.

N-Acylbenzotriazoles **4d** and **4e** with a Reformatsky reagent prepared *in situ* gave the corresponding ethyl esters of arylcarboxylic acids **8a,b** in moderate yields, probably *via* six-membered cyclic transition state **7** (Scheme 3).



Scheme 3

The possible application of catalysts based on other transition metals was studied using 2-furylcarbonylbenzotriazole **4f** as a model compound. The results of the reaction of **4f** with prepared *in situ* *n*-PrZnI in the presence of $NiCl_2$, instead of $PdCl_2(PPh_3)_2$, in various reaction conditions are summarized in Table 3. However, even the best yield obtained (entry 7) is significantly lower than the one obtained with palladium catalyst (25% *vs*. 55%), although in the first case the reaction is much faster. The reaction of *N*-benzoylbenzotriazole **4d** with *n*-propylzinc iodide under the reaction conditions shown in entry 7 gave propyl benzoate in surprisingly high 46% yield. The application of iron(III) acetylacetonate as a transition metal catalyst was less successful: in its presence the reaction of **4f** with *n*-PrZnBr gave propyl 2-furoate **6e** in only 20% yield.

Table 3. Reaction conditions optimization for the reaction of *N*-acylbenzotriazole **4f** with *n*-PrZnI in the presence of $NiCl_2$

Reaction conditions						
Entry	$NiCl_2$	Zn (dust)	$ZnBr_2$	Solvent	Time, h	Yield of **6e**, %
1	1 equiv	+	−	DMF	6	decomposition
2	1 equiv	+	−	THF	4	traces
3	10 mol %	+	1 equiv	toluene	24	no reaction
4	10 mol %	−	1 equiv	THF	40	22%*
5	10 mol %	+	1 equiv	THF	19	22%
6	catalyt.	+	1 equiv	THF	65	22%
7	10 mol %	+	1 equiv	THF / toluene	18	25%

- some starting material was recovered

During our work with $NiCl_2$ as a catalyst, we observed that in the presence of 1 equiv of Zn dust a reaction achieves its completion significantly faster than when only traces of metallic Zn, brought in with an organozinc reagent, were present in the reaction mixture (cf. entries 4 and 5, Table 3). This led us to the conclusion that Ni(0) species, formed *in situ* by the reduction of $NiCl_2$ with Zn dust, but not Ni(II) species, is the active catalytic form. Therefore, we investigated the effect of the direct introduction of the commercially available Ni(0) catalyst, $Ni(COD)_2$. The results of a series of reactions of *N*-acylbenzotriazoles with organozinc reagents in the presence of $Ni(COD)_2$ are given in Table 2. As follows from these results, the catalysis with $Ni(COD)_2$ affords the corresponding esters in the yields comparable to those obtained with Pd(II) catalyst. Moreover, the reactions with aliphatic organozinc reagents catalyzed with a Ni(0) catalyst (either $Ni(COD)_2$ or the one, formed *in situ* from $NiCl_2$) have considerably higher reaction rates (for example, compare entries 6 and 11, Table 2).

In summary, we have shown that on treatment with an organozinc reagent in the presence of zinc bromide and a catalytic amount of a transition metal catalyst [Pd(II) or Ni(0)], *N*-acylbenzotriazoles undergo unexpected transformation into the corresponding carboxylic acid esters.

Experimental Section

General Procedures. Melting points were measured on a Mel-Temp capillary melting point apparatus equipped with a Fluka 51 digital thermometer and are uncorrected. ^1H and ^{13}C NMR data were recorded on Gemini 300 MHz NMR spectrometer (300 and 75 MHz, respectively) in $CDCl_3$ as a solvent and with TMS as an internal standard. Column chromatography was carried out on silica (200-425 mesh, Fisher). *N*-Acylbenzotriazoles **4a-e**[24] and **4f-h**[25] were prepared according to the literature procedures. Benzylzinc bromide[29] and alkylzinc halides[30] were prepared by standard reaction of activated zinc dust with the corresponding halides (for the procedure of the preparation of activated zinc dust see 31).

1-(Furyl-3-carbonyl)benzotriazole (4g). white needles (from methanol), mp 91−92°C, ^{1}H NMR δ 7.19 (d, *J* = 2.0 Hz, 1H), 7.47−7.57 (m, 2H), 7.65 (t, *J* = 7.2 Hz, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 8.35 (d, *J* = 8.3 Hz, 1H), 8.81 (s, 1H); ^{13}C NMR δ 111.2, 114.6, 119.4, 120.0, 126.1, 130.3, 131.8, 143.5, 145.6, 151.2, 160.1. Anal. Calcd. for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 61.75; H, 3.12; N, 19.75.

1-(Thiophen-2-ylcarbonyl)benzotriazole (4h). white needles (from methanol), mp 172−173°C, ^{1}H NMR δ 7.27 (dd, *J* = 4.9, 3.9 Hz, 1H), 7.53 (t, *J* = 8.3 Hz, 1H), 7.68 (t, *J* = 8.3 Hz, 1H), 7.88 (dd, *J* = 4.9, 1.2 Hz, 1H), 8.15 (d, *J* = 8.3 Hz, 1H), 8.38 (d, *J* = 8.3 Hz, 1H), 8.57 (dd, *J* = 3.9, 1.2 Hz, 1H); ^{13}C NMR δ 114.8, 120.2, 126.3, 128.1, 130.4, 132.1, 133.3, 137.2, 138.4, 145.7, 159.2. Anal. Calcd. for $C_{11}H_7N_3OS$: C, 57.61; H, 3.08; N, 18.33. Found: C, 57.58; H, 2.94; N, 18.24.

General procedure for the synthesis of esters 6a-i and 8a,b in the presence of Pd(II) or Ni(0) catalyst

A solution of organozinc halide, prepared *in situ* from the corresponding benzylic or aliphatic halide (4 mmol) and activated zinc dust (0.40 g, 6 mmol) in dry THF (20 mL), was decanted under nitrogen from the residual zinc metal and added dropwise at rt to a mixture of a *N*-acylbenzotriazole **4** (2 mmol), anhydrous zinc bromide (0.51 g, 2 mmol) and a catalytic amount of the transition metal catalyst [$PdCl_2(PPh_3)_2$ or $Ni(COD)_2$] in dry toluene (30 mL). The reaction mixture obtained was heated under reflux under nitrogen until the reaction completion (TLC control; for the reaction time required in each particular case see Table 2). Then the reaction mixture was allowed to cool down and was treated successively with aqueous NH_4Cl (2 x 30 mL), water (50 mL), aqueous Na_2CO_3 (2 x 30 mL) and water (50 mL). The organic fraction was dried over $MgSO_4$. The yellow oily residue obtained after solvent removal *in vacuo* was further subjected to the column chromatography purification (gradient eluation with hexanes to ethyl acetate : hexane = 1:3).

Benzyl acetate (6a). colorless liquid,[32] yield 58%; ^{1}H NMR δ 2.10 (s, 3H), 5.11 (s, 2H), 7.30−7.50 (m, 5H); ^{13}C NMR δ 21.0, 66.3, 128.2, 128.3, 128.5, 135.9, 170.8 (one signal is overlapped).

Benzyl benzoate (6b). colorless liquid,[33] yield 70%; ^{1}H NMR δ 5.35 (s, 2H), 7.32−7.45 (m, 7H), 7.49−7.52 (m, 1H), 8.07 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR δ 66.6, 128.1, 128.2, 128.3, 128.5, 129.6, 130.0, 132.9, 135.9, 166.3.

Benzyl anisate (6c). colorless liquid,[34] yield 62%; ^{1}H NMR δ 3.86 (s, 3H), 5.34 (s, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.30−7.50 (m, 5H), 8.03 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR δ 55.3, 66.3, 113.5, 122.4, 128.0, 128.1, 128.5, 131.6, 136.2, 163.3, 166.1.

Benzyl 2-furoate (6d). colorless liquid,[35] yield 67%; ^{1}H NMR δ 5.33 (s, 2H), 6.48 (dd, *J* = 3.4, 1.6 Hz, 1H), 7.19 (d, *J* = 3.4 Hz, 1H), 7.28−7.46 (m, 5H), 7.56 (s, 1H). ^{13}C NMR δ 66.5, 111.8, 118.1, 126.5, 128.3, 128.5, 135.5, 144.5, 146.4, 158.5.

***n*-Propyl 2-furoate (6e).** colorless liquid,[36] yield 55%; ^{1}H NMR δ 1.01 (t, *J* = 7.5 Hz, 3H), 1.72−1.85 (m, 2H), 4.27 (t, *J* = 6.8 Hz, 2H), 6.50 (dd, *J* = 3.3, 1.6 Hz, 1H), 7.17 (d, *J* = 3.3 Hz, 1H), 7.58 (s, 1H); ^{13}C NMR δ 10.3, 22.0, 66.4, 111.7, 117.6, 144.8, 146.1, 158.7.

***i*-Propyl 2-furoate (6f).** colorless liquid,[37] yield 53%; ^{1}H NMR δ 1.36 (d, *J* = 6.3 Hz, 6H), 5.22−5.29 (m, 1H), 6.50 (dd, *J* = 3.4, 1.7 Hz, 1H), 7.16 (d, *J* = 3.4 Hz, 1H), 7.58 (s, 1H); ^{13}C NMR δ 21.7, 68.4, 111.6, 117.4, 145.0, 145.9, 158.2.

Benzyl 2-thenoate (6g). colorless liquid,[38] yield 81%; ^{1}H NMR δ 5.31 (s, 2H), 7.04 (dd, *J* = 5.0, 3.8 Hz, 1H), 7.14−7.20 (m, 1H), 7.23−7.30 (m, 1H), 7.30−7.44 (m, 3H), 7.49 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.80 (dd, *J* = 3.7, 1.2 Hz, 1H); ^{13}C NMR δ 66.6, 125.8, 128.0, 128.2, 128.3, 128.5, 132.4, 133.5, 135.7, 161.9.
Benzyl 3-furoate (6h). colorless liquid,[39] yield 52%; ^{1}H NMR δ 5.29 (s, 2H), 6.76 (d, *J* = 1.1 Hz, 1H), 7.35−7.42 (m, 6H), 8.04 (s, 1H); ^{13}C NMR δ 66.1, 109.8, 119.2, 128.1, 128.2, 128.5, 135.9, 143.7, 147.8, 162.8.
***n*-Propyl 3-furoate (6i).** colorless liquid,[40] yield 44%, ^{1}H NMR δ 0.99 (t, *J* = 7.4 Hz, 3H), 1.70−1.78 (m, 2H), 4.21 (t, *J* = 6.7 Hz, 2H), 6.75 (d, *J* = 1.4 Hz, 1H), 7.42 (pseudo-t, *J* = 1.4 Hz, 1H), 8.02 (s, 1H); ^{13}C NMR δ 10.2, 21.9, 65.8, 109.7, 119.5, 143.5, 147.4, 163.0.
Ethyl benzoate (8a). colorless liquid,[41] yield 50%; ^{1}H NMR δ 1.31 (t, *J* = 7.1 Hz, 3H), 4.30 (q, *J* = 7.1 Hz, 2H), 7.33−7.42 (m, 2H), 7.55−7.42 (m, 1H), 7.97 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR δ 14.3, 60.9, 128.3, 129.5, 130.5, 132.7, 166.6.
Ethyl anisate (8b). colorless liquid,[42] yield 48%; ^{1}H NMR δ 1.38 (t, *J* = 7.1 Hz, 3H), 3.85 (s, 3H), 4.34 (q, *J* = 7.1 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.99 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR δ 14.3, 55.3, 60.6, 113.5, 122.9, 131.5, 163.2, 166.3.

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