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Nucleophilic substitution reactions of aminoalkylbenzotriazoles with ytterbium metal umpoled diaryl ketones

Weike Su,[a,]* Bibo Yang[a] and Yongmin Zhang[b]

[a]*College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, PR China*
[b]*Department of Chemistry, Zhejiang University (Campus Xixi), Hangzhou 310028, PR China*

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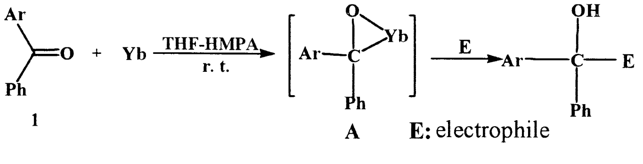
Abstract—The reaction of diaryl ketones such as benzophenone with aminoalkylbenzotriazoles in the presence of ytterbium metal at room temperature has been found to give 2-amino alcohols in good yields under mild and neutral conditions. © 2002 Elsevier Science Ltd. All rights reserved.

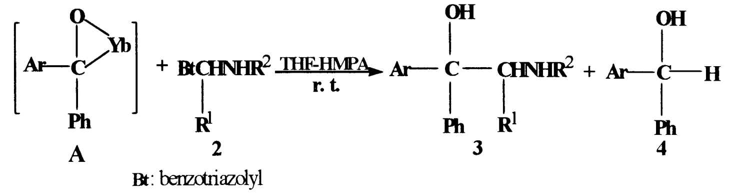
Lanthanoid reagents, especially samarium reagents, have been extensively utilized in organic synthesis because of their unique properties.[1] For example, the strong reducing ability of low-valent lanthanoids allows the easy reduction of many functional groups and provides a convenient method for reductive carbon–carbon bond formation.[2] Oxophilicity and the high coordination numbers of trivalent lanthanoids have enabled them to act as new Lewis acids.[3] However, studies on the applications of ytterbium metal in organic synthesis are relatively few. Hou et al. have reported that the carbonyl carbons of diaryl ketones could be umpoled by the reaction with ytterbium metal and the ytterbium–benzophenone dianionic complexes thus formed were successfully characterized by X-ray analyses.[4] The anionic carbonyl carbons were nucleophilic and were coupled with various electrophiles such as ketones, nitriles, epoxides, carbon dioxide, etc.,[5] to give the corresponding products (Scheme 1).



Scheme 1.

Here we wish to report the nucleophilic substitution reaction of aminoalkylbenzotriazoles with ytterbium metal umpoled diaryl ketones in which the carbonyl groups are umpoled by ytterbium from electrophilic to nucleophilic (Scheme 2). The results are shown in Table 1.

From Table 1, it can be seen that the substitution pattern of the phenyl R^2 strikingly affected the yields of products **4**. The yields for substrates without substituents and with substituents in a *para*-position were much higher than those with the substituents in *meta*- and *ortho*-positions (entries 1, 5, 6 and 7). Prolonged reaction times and increased reaction temperatures



Scheme 2.

Keywords: ytterbium; nucleophilic substitution; aminoalkylbenzotriazoles.

* Corresponding author.

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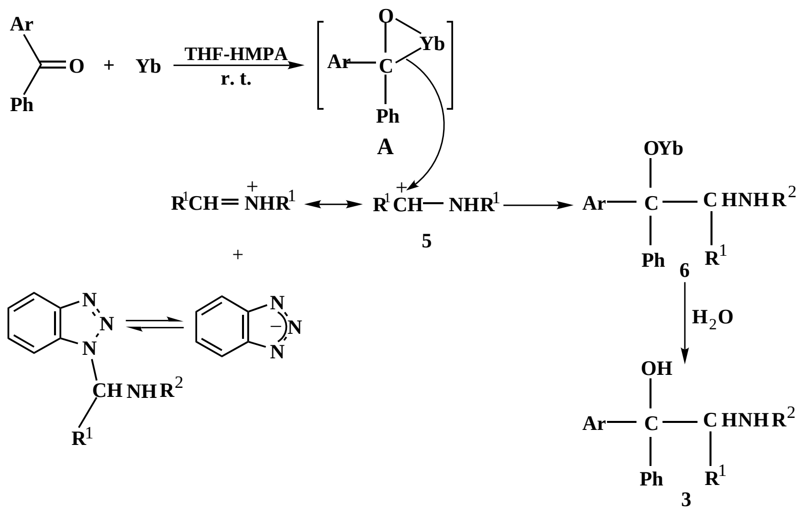
Table 1. Ytterbium metal promoted reaction of diaryl ketones with aminoalkylbenzotriazoles[6]

Entry	Ar	R^1	R^2	Time (h)	Yield[a] (%)	
1	C_6H_5	H	C_6H_5	1	76 (**3a**)	21 (**4a**)
2	C_6H_5	H	*p*-$MeOC_6H_4$	2	68 (**3b**)	29 (**4b**)
3	C_6H_5	Et	*p*-ClC_6H_4	2	67 (**3c**)	28 (**4c**)
4	C_6H_5	Et	*p*-$MeOC_6H_4$	2	65 (**3d**)	31 (**4d**)
5	C_6H_5	H	*m*-MeC_6H_4	14	29 (**3e**)	68 (**4e**)
6	C_6H_5	H	*o*-EtC_6H_4	26	Trace (**3f**)	92 (**4f**)
7	C_6H_5	H	*o*-ClC_6H_4	26	Trace (**3g**)	94 (**4g**)
8	C_6H_5	C_6H_5	C_6H_5	2	71 (**3h**)	23 (**4h**)
9	*p*-MeC_6H_4	Et	*p*-$MeOC_6H_4$	1	63 (**3i**)	32 (**4i**)
10	*p*-MeC_6H_4	C_6H_5	*p*-ClC_6H_4	2	62 (**3j**)	35 (**4j**)
11	*p*-ClC_6H_4	Et	*p*-ClC_6H_4	2	78 (**3k**)	20 (**4k**)
12	*p*-ClC_6H_4	C_6H_5	*p*-$MeOC_6H_4$	1	76 (**3l**)	21 (**4l**)

[a] Isolated yield based on aminoalkylbenzotriazoles.



Scheme 3.

scarcely improved the yields of products. Presumably the increased steric hindrance prevented the nucleophilic substitution.

Aryl alkyl ketones and dialkyl ketones cannot be used in this reaction because of the low stability of the intermediates (**A**).[7]

The mechanism for the nucleophilic substitution reactions of aminoalkylbenzotriazoles with ytterbium metal umpoled diaryl ketones is not clear at present. According to Ref. 5b and considering benzotriazolyl as being an excellent leaving group, a possible mechanism is shown in Scheme 3. Aminoalkylbenzotriazoles have been shown to exist in equilibrium with an iminium cation in solution.[8] Ytterbium metal reacts with benzophenone to give the ytterbium–benzophenone dianionic complexes (**A**). The complexes (**A**) acting as nucleophilic reagents attack the electrophilic center of the iminium cations **5** to generate the intermediates **6**. The corresponding amino alcohols **3** are obtained after hydrolysis.

In conclusion, with good yields, mild and neutral conditions as well as a straightforward procedure, the work described herein provides a useful method for the preparation of 2-amino alcohols. Further studies to develop other new reactions using the ytterbium–benzophenone dianionic complexes (**A**) are now in progress.

Acknowledgements

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6. *General procedure*: In a 25 mL flask were placed Yb metal powder (40 mesh, 1 mmol) and a magnetic stirring bar. The flask was sealed with a serum cap. Pure and dry nitrogen was then passed through and the metal was dried by heating under a stream of nitrogen. One drop of methyl iodide was added via a micro syringe and the metal was heated slightly using a heat gun to activate the Yb metal. Addition of THF (2 mL) gave a pale yellow slurry to which HMPA (1 mL) was introduced. An appropriate amount of diaryl ketone in THF (2 mL) was then added and the solution immediately turned dark blue. The mixture was then stirred at room temperature for a few minutes and a purple solution was finally obtained, and then aminoalkylbenzotriazoles **2** (1 mmol in THF, 2 mL) was added. The mixture was stirred at room temperature for the given time (see Table 1). The products were treated with 0.1 M HCl (5 mL) and then extracted with diethyl ether (3×30 mL). The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. After the solvent was evaporated under reduced pressure, the crude products were purified by preparative TLC on silica gel using ethyl acetate–cyclohexane (1:8) as eluent. Compound **3a**, oil. ν_{max}/cm^{-1}: 3504, 3401, 2866, 1602, 1503. δ_H: 6.60–7.51 (15H, m, ArH), 5.76 (2H, s, CH_2), 3.86 (1H, s, OH), 3.29 (1H, br s, NH). MS (*m*/*z*,%): 290 (M^++1, 19), 289 (M^+, 4), 272 (23), 183 (10), 107 (63), 106 (100), 105 (43), 77 (38). Anal. $C_{20}H_{19}NO$. Calcd C, 83.04; H, 6.57; N, 4.84. Found C, 83.12; H, 6.51; N, 4.79%. Compound **3j**, mp 140–142°C. ν_{max}/cm^{-1}: 3550, 3429, 1670, 1175. δ_H: 6.26–7.55 (18H, m, ArH), 5.21 (1H, s, CH), 4.60 (1H, br s, OH), 2.90 (1H, s, NH), 2.30 (3H, s, CH_3). MS (*m*/*z*,%): 414 (M^++1, 3), 396 (2), 218 (34), 217 (21), 216 (100), 138 (26), 111 (16), 105 (29), 91 (16), 77 (28). Anal. $C_{27}H_{24}ClNO$. Calcd C, 78.26; H, 5.80; N, 3.38. Found C, 78.20; H, 5.71; N, 3.42%.

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