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One-Pot Synthesis of *N*-Alkyl Benzotriazoles via a Brønsted Acid-Catalyzed Three-Component Reaction

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Abstract. A novel three-component condensation reaction of benzotriazoles, aldehydes and tertiary anilines efficiently catalyzed by readily available organic acid *p*-toluenesulfonic acid (PTSA) has been developed. A series of *N*-alkyl benzotriazoles were synthesized in up to 97% yield for 21 examples starting from anilines, benzotriazoles and formaldehyde. This strategy features a simple system, atom economy, environmental friendliness, high efficiency, excellent regioselectivity, good functional group tolerance, easily available starting materials, and cheap catalyst. The mechanistic studies indicated that aza quinone methide was probably involved as an intermediate in this transformation.

Keywords: C-H bond activation; Brϕnsted Acid-catalyzed; Aminomethylation; Three-component reaction

C–H bond functionalization has emerged as a powerful tool for organic synthesis due to its atom economy and efficiency.[1] Among all the challenges, the regio-selectivity is always a major problem. In this context, directing group (DG)-assisted transition metal-catalyzed C-H bond activation has been developed, in which the access to *ortho*-functionalized targets has been achieved in most cases.[2] However, the development of general protocols for the remote selective C–H functionalization is still demanding. Yu group has reported the selective *meta* olefination, arylation, acetoxylation, and iodination of arene via a highly strained, tricyclic cyclophane-like transition state using an easily removable U-shaped template. [3a-3d] Then, Maiti developed a Pd-catalyzed direct *para*-olefination and acetoxylation of arenes with a biphenyl-silyl-tethered D-shaped assembly. [3e-3f] An alternative strategy is using norbornene as a ligand in the selective C-H bond activation, as reported by Catellani group.[4] The key step of this transformation is formation of a five-membered, norbornene-bridged palladacycles through *ortho* C−H activation of the aryl halides. Inspired by this unique reactivity of norbornene in palladium-catalyzed reactions, remarkable progress has been developed to achieve *meta*-selective alkylation, chlorination and arylation of arenes.[5-6] Very recently, Ackermann and co-workers reported a Ru catalyzed *meta*-selective functionalization of 2-phenylpyridines *via* ArS_E process, in which the specific selectivity is determined by the electronic structure of the transition state.[7] However, transition-metal catalysts were required in these procedures, and they might cause the potential contamination of the products, which causes significant problems in pharmaceutical industry. In the meantime, the metal-free catalytic remote C−H functionalization has been scarcely reported,[8] and its development is highly desired.

Anilines could be transformed into an active intermediate, aza quinone methides, in the presence of formaldehyde under acidic condition, which is formed *via* regioselective Friedel-Crafts-type reaction of anilines with formaldehyde at the *para*-position.[9] Most of these reports focused on the formation of C-C bond. We envisioned that the reaction of aza quinone methide with benzotriazoles would probably form a new C–N bond and, therefore, provide a new approach to achieve *para*-selective C-H aminomethylation of anilines, which does not require a coordinating DG. On the other hand, benzotriazole is a privileged heterocycle and key skeleton in bioactive molecules, photosensitive compositions, and dyes. For example, they have presented in antibacterials,[10] antifungal agents,[11] antineoplastic agents,[12] anticancer,[13] HIV inhibitors[14] and benzotriazole-based azo dyes.[15] In despite of their versatile biologicalactivities, there are only a few reports on the synthesis of such compounds and limited to a few specific examples.[16] Herein, we present the synthesis of benzotriazole derivatives starting from anilines, benzotriazoles and formaldehyde catalyzed by easily available *p*-toluenesulfonic acid (PTSA). This protocol is highly regioselective, efficient, and environmental friendly.

To test above hypothesis, we investigated the three-component reaction of benzotriazole **1a**, formaldehyde **2a**, and *N*,*N*-dibenzylaniline **3a** in the presence of 0.1 equiv $FeCl_3$. The desired product **4a** was obtained in 29% yield (entry 1, Table 1). This results encouraged us to screen various reaction

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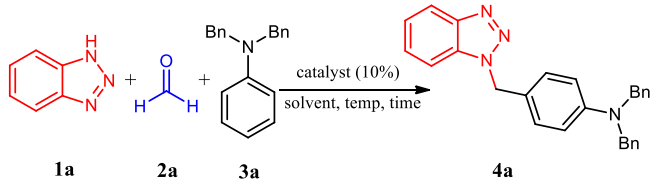
Table 1. Optimizing Various Parameters for the Condensation of *N*,*N*-Dibenzylaniline, Formaldehyde with Benzotriazolea

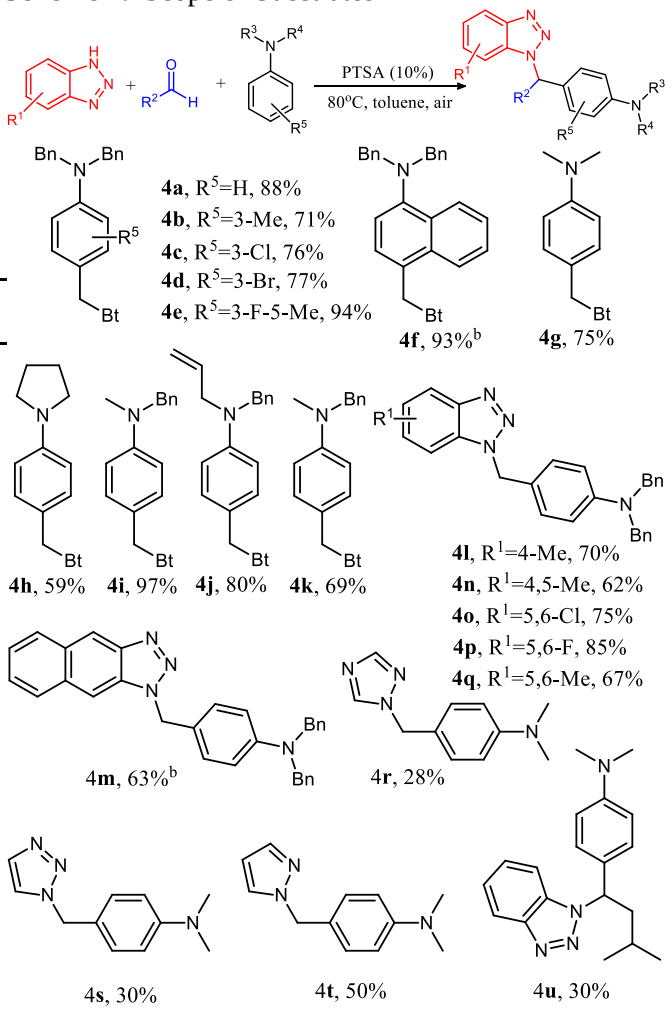


1a 2a 3a 4a

Entry	Catalyst (10%)	T (°C)	Solvent	t (h)	Yield (%)[b]
1	$FeCl_3$	80	toluene	10	29
2[c]	$Fe(acac)_3$	80	toluene	10	N.R
3[d]	$FeCl_2$	80	toluene	10	37
4	$ZnCl_2$	80	toluene	10	trace
5	$AlCl_3$	80	toluene	10	47
6	$BF_3{\cdot}Et_2O$	80	toluene	10	37
7	H_2SO_4	80	toluene	10	10
8	HCl	80	toluene	2	28
9	AcOH	80	toluene	10	N.R
10	CF_3COOH	80	toluene	10	70
11	**TsOH**	**80**	**toluene**	**2**	**88**
12	TfOH	80	toluene	10	51
13	TsOH	80	DMF	2	32
14	TsOH	80	DMSO	2	66
15	TsOH	80	CH_3CN	2	trace
16	TsOH	80	C_2H_5OH	2	35
17	TsOH	80	dioxane	2	63
18	TsOH	60	toluene	2	65
19	TsOH	10	toluene	2	59

Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), **3a** (0.24 mmol), catalyst (10 mol %), solvent 2 mL under air; isolated yields. [b] isolated yield. [c] under air. [d] under N_2.

Scheme 1. Scope of Substrates [a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), **3** (0.24 mmol), catalyst (10 mol %), toluene 2 mL under air. [b]100°C. Bt = benzotriazole. Bn=benzyl.

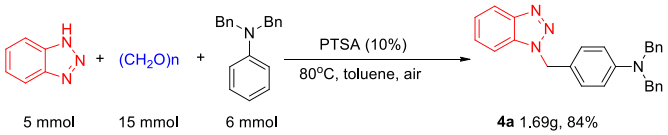
parameters, as shown in Table 1. Lewis acids, such as $FeCl_2$, $Fe(acac)_2$, $ZnCl_2$, $AlCl_3$, $BF_3{\cdot}Et_2O$ were tested firstly, with the highest yield of 47% using $AlCl_3$ (entries 2-6). Then the strong brønsted acids were valuated (entries 7-8 and 10-12). TsOH was found to favor this transformation and afforded **4a** in 88% yield. While no product was detected when weak acids, such as AcOH was used (entry 9). The solvents were subsequently investigated and toluene turned out to be the best (entries 13−17). Decreasing or increasing the reaction temperature resulted in lower yields (entries 18-19). Finally, the optimized reaction conditions were identified as follows: **1a** (0.2 mmol), **2a** (0.6 mmol), **3a** (0.24 mmol), 0.1 equiv of PTSA as the catalyst under air in toluene at 80 °C for 2h.

With the optimized reaction conditions in hand, we investigated the scope of the substrates (Scheme 1). A variety of *N*,*N*-dibenzylanilines with electron-donating or electron withdrawing groups on the phenyl rings were studied. The corresponding products **4a**-**4e** were obtained in good to excellent yields. It is worth noting that the desired product **4e** was obtained in 94% yield from steric bulky substrate 3-floro-5-methyl-*N*,*N*-dibenzylaniline **3e**. Dibenzylnaphthylamine was also a suitable substrate, providing target product **4f** in 93% yield at 100 °C. Halogens, including F, Cl and Br, were all well-tolerated (**4c**-**4e**), thus affording more opportunities for further transformations. Subsequently, a variety of tertiary anilines with different nitrogen substitutions were tested. *N*,*N*-dimethylaniline and 1-phenylpyrrolidine afforded **4g** and **4h** in 75% and 59% yields, respectively. *N*-Benzyl-*N*-methylanilines worked very well and produced the desired product in 97% yield (**4i**). *N*-Allyl and *N*-isopropyl anilines were also applied and gave the desired products in good yields (**4j** and **4k**).

Substituted benzotriazoles were also investigated and the corresponding products (**4l**-**4q**) were obtained in good yields. Moreover, naphthotriazole was a suitable substrate, affording the corresponding product in 63% yield (**4m**). In addition, simple azoles and aliphatic aldehydes could also be applied to this reaction system, despite of lower yields (**4r**-**4u**).

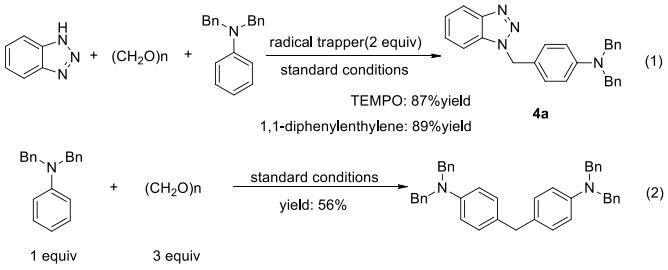
To prove the practicality of this metal-free aminomethylation reaction, a gram scale reaction has been performed (Scheme 2). When 0.595 g of benzotriazole, 60 mg formaldehyde and 1.64 g *N*,*N*-dibenzylaniline were loaded under the standard reaction conditions, product **4a** was obtained in 84% yield (1.69 g).

Scheme 2. Gram-Scale Reaction



To clarify the reaction mechanism of this *para*-selective aminomethylation process, some control experiments were carried out. The radical scavengers, TEMPO (2,2,6,6-tetramethyl piperidine 1-oxyl) and 1,1-diphenylethylene, did not inhibit this transformation (Scheme 3, eq 1), indicating that a radical pathway might not be involved in this process. In the absence of benzotriazole, *N*,*N*-dibenzylaniline reacted with formaldehyde under standard conditions and gave diarylmethane in 56% yield (Scheme 3, eq 2), which probably formed through aza quinone methide intermediate. In addition, no reaction was observed by combining benzotriazole with formaldehyde under the standard reaction conditions.

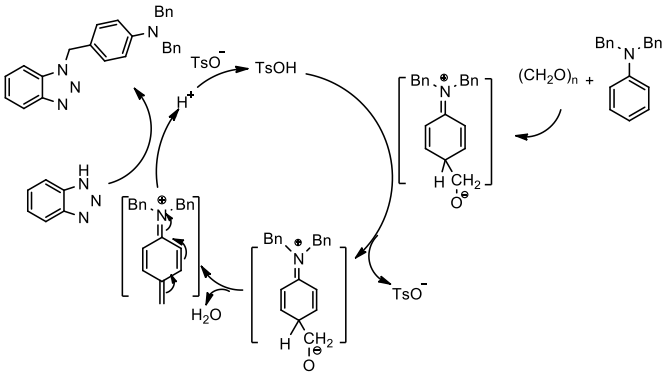
Scheme 3. Control Experiments



Based on the literatures[17] and aforementioned observations, a tentative reaction mechanism was proposed, as depicted in Scheme 4. First, a Brϕnsted acid catalyzed regioselective Friedel-Crafts type reaction of aniline with formaldehyde and it is followed by dehydration to give aza quinone methide intermediate. The nucleophilic attack of benzotriazole on the aza quinone methide then produced the target product.

In summary, we have realized a three-component reaction of anilines, benzotriazoles and aldehydes for the synthesis of *N*-benzyl benzotriazoles, using PTSA as a catalyst. The reaction could be carried without inert gas protection, and generate 1 equiv of H_2O as the sole byproduct. This protocol exhibited an excellent performance in terms of atom economy and environmental friendliness. Moreover, this investigation would provide a new strategy to construct the novel molecule library for drug development.

Scheme 4. Proposed Reaction Mechanism



Experimental Section

Typical Procedure

Benzotriazole (0.2 mmol), 0.6 mmol formaldehyde and 0.24 mmol *N*,*N*-dibenzylaniline were added into the flask charged with 0.02 mmol PTSA in toluene solvent (2 ml). The mixture was stirred at 80 °C for 2 h, then cooled down to room temperature, diluted with 10 mL dichloromethane and washed with 10 mL H_2O. The aqueous layer was extracted twice with dichloromethane (5 mL) and the combined organic phase was dried over anhydrous $MgSO_4$. After evaporation of the solvents, the residue was purified by silica gel chromatography or thin layer chromatography (TLC) (eluent: petroleumether-EtOAc).

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UPDATES

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

TOC Graphic

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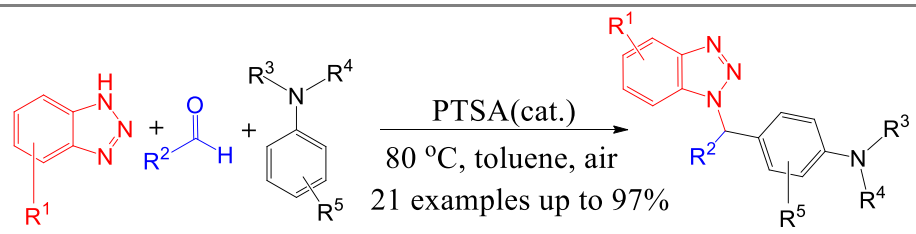

R^1=alkyl, F, Cl
R^2=alkyl
R^3=R^4=alkyl, naphthene, alkylene
R^5=alkyl, F, Cl, Br
PTSA=*p*-toluene sulfonic acid

- Gram scale
- Metal free
- Air atmosphere
- Three components in one-pot
- Water as byproduct