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I_2-Catalyzed Oxidative Coupling Reactions of Hydrazones and Amines and the Application in the Synthesis of 1,3,5-Trisubstituted 1,2,4-Triazoles

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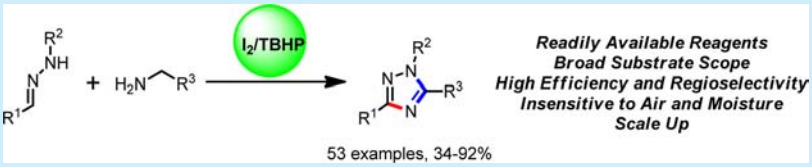
Supporting Information



ABSTRACT: A general and expeditious approach for the metal-free mediated synthesis of 1,3,5-trisubstituted 1,2,4-triazoles from hydrazones and aliphatic amines has been achieved under aerobic oxidative conditions. The reaction proceeds through a cascade C−H functionalization, double C−N bonds formation, and oxidative aromatization sequence.

1,2,4-Triazoles, as highly privileged heterocyclic scaffolds, have found extensive applications in biological and pharmaceutical fields as well as materials science.[1] Several potent biological activities, such as antihypertensive, antifungal, and antibacterial activities,[2] have aroused considerable attention among medicinal chemists. 1,2,4-Triazole scaffolds were found in valuable pharmaceuticals, including maraviroc, trizaolam, sitagliptin, and deferasirox.[3] Furthermore, 1,2,4-triazoles have also been investigated as versatile ligands for metal coordination, displaying immense application prospects.[4] On the other hand, research on 1,3,5-triaryl substituted *1H*-1,2,4-triazoles has attracted much interest in materials science including application in the fields of solar cells, image sensors, dye lasers, and electroluminescent devices.[5] Therefore, general and straightforward methods to their synthesis are of great significance, and a series of synthetic strategies of 1,2,4-triazoles have been developed.

The Pellizzari reaction[6] and Einhorn−Brunner reaction[7] are traditional methods for the preparation of 1,2,4-triazole motifs under transition-metal-free conditions but are limited due to their poor regioselectivities. A frequently used synthetic method was intramolecular cyclodehydration of *N*-acylamidrazone derivatives, which could be accessed from diverse synthetic precursors;[8] the alternative pathway utilized the hydrazonyl chloride as a common synthetic intermediate.[9] Treatment of hydrazonyl chloride with nitrile in the presence of $AlCl_3$ at elevated temperature or with a primary amine under basic and oxidative conditions could lead to a 1,2,4-triazole product in moderate yield. Apart from these pioneering works, a myriad of other useful methods for the preparation of 1,2,4-triazoles have been disclosed.[10] However, most of the existing methods suffered from multistep synthetic procedures, inferior regioselectivity, a narrow substrate scope, and limited functional group tolerance. Pertinent to the present research, the development of a one-pot regioselective approach for the efficient construction of the 1,2,4-triazole structure is highly desirable.

Recently, considerable progress in oxidative C−H functionalization by metal-free approaches has been attained. Owing to its diverse oxidation states and moderate redox potential, molecular iodine has been widely applied as a good activator in a range of chemical transformations, especially in oxidative coupling reactions.[11] Extensive investigations of the iodine/peroxide combination mediated oxidative reaction have led to the vigorous development of an array of useful synthetic methodologies.[12] Although significant advancement has been made in the fascinating field, the exploration and development of highly efficient catalytic transformations via a nonmetallic iodine mediated strategy for the synthesis of valuable heterocyclic molecules are still attractive and promising. Herein, we report an unprecedented, mild, and operationally simple approach for the assembly of structurally diverse 1,3,5-trisubstituted 1,2,4-triazoles from readily accessible hydrazones and amines under metal-free conditions.

We chose bisarylhydrazone **1a** and 4-methyl-benzylamine **2b** as model substrates to start our study. The corresponding hydrazones could be prepared quite conveniently from the simple condensation of relevant aldehydes and hydrazines in ethanol. The reaction between bisarylhydrazone **1a** and 4-methyl-benzylamine **2b** in the presence of 10 mol % I_2 and 3 equiv of TBHP in dioxane at 90 °C was initially examined. To our delight, the desired cyclized product 1,3-diphenyl-5-(*p*-tolyl)-1*H*-1,2,4-triazole **3b** was formed in 40% yield (see entry 1 in Table S1 in the Supporting Information). Further investigation toward the amount of iodine revealed that the combination of 20 mol % I_2 and 3 equiv of TBHP could give the best efficiency (Table S1, entries 2−4). A dramatic reduction in reaction yield was observed in the absence of iodine, highlighting the crucial role of iodine (Table S1, entry 5). The solvent effect of the reaction was tested

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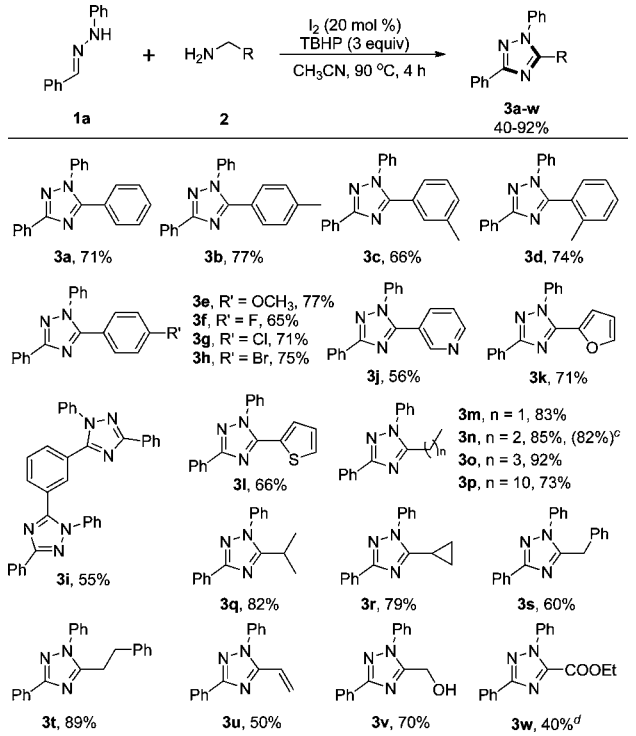
by the use of different solvents, and CH_3CN was identified as the optimal choice, giving the highest yield of the reaction (Table S1, entries 6−11). The replacement of iodine with another iodine-containing activator, including KI, NIS, or TBAI, resulted in a slight decrease in the reactivity of the reaction (Table S1, entries 12−14). When other commonly used oxidants, such as TBPB, DTBP, H_2O_2, and BPO, were employed in the reaction, the conversion of the reaction was clearly inferior to that of TBHP (Table S1, entries 15−18). An inert atmosphere could inhibit the reaction to a lesser extent (Table S1, entry 19). It turned out that implementation of the reaction at ambient temperature, 60 or 120 °C, could achieve comparable reactivity, albeit in moderately lower yield (Table S1, entry 20).

With the optimal reaction conditions in hand, the scope and limitation of the oxidative synthesis of 1,2,4-triazoles were next investigated (Scheme 1). A variety of benzylamines bearing

Scheme 1. Synthesis of 1,2,4-Triazoles from Diverse Amines[a,b]

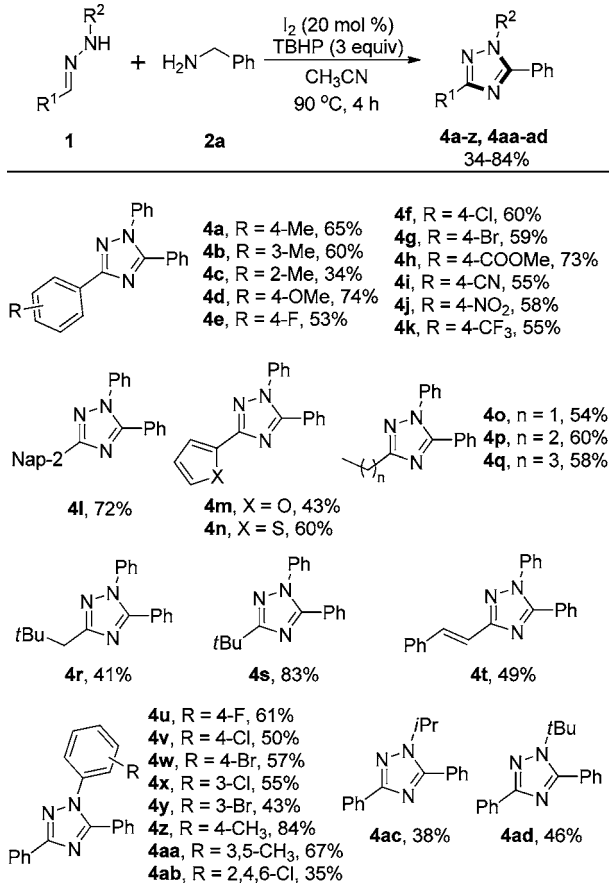


[a]Reaction conditions: **1a** (0.3 mmol), amine **2** (0.9 mmol), I_2 (20 mol %), and TBHP (0.9 mmol) in CH_3CN (1 mL) under air at 90 °C for 4 h. [b]Isolated yield. [c]The reaction was performed on 10 mmol scale. [d]**1a** (0.3 mmol), glycine ethyl ester hydrochloride **2w** (0.6 mmol), I_2 (20 mol %), K_2CO_3 (0.3 mmol), and TBHP (0.9 mmol) in CH_3CN (1 mL) under air at 30 °C for 4 h.

electron-donating or -withdrawing groups were subjected to the standard conditions, and moderate to good yields could be attained (**3a−h**). It was worth mentioning that steric hindrance (**3b−d**) and electronic factors (**3a−h**) of benzylamines seemingly exerted a negligible influence on the reaction. When the 1,3-phenylenedimethanamine was used as the starting reactant for the reaction, the desired product **3i** containing two 1,2,4-triazole rings was isolated in reasonable yield. Some heterocyclic moieties, including pyridine, furan, and thiophene, could be smoothly incorporated in the 1,2,4-triazole molecule by using corresponding heterocyclic amines (**3j−l**). More importantly, various linear aliphatic amines were also compatible with the reaction system with higher efficiency than that of benzylamines, further expanding the structural diversity of the obtained 1,2,4-triazoles (**3m−t**). It should be noted that the catalytic transformation was reproducable on a gram scale without any difficulty (**3n**). Interestingly, the allylamine could be applied as a viable substrate in the reaction to produce 5-allyl substituted 1,2,4-triazole **3u** in acceptable yield. Noteworthy was that a free hydroxyl group could be introduced into the 1,2,4-triazole ring **3v** by the use of 2-aminoethanol as the reactant. The amino acid derivative such as glycine ethyl ester hydrochloride could also undergo the transformation at room temperature to lead to 5-ethoxycarbonyl substituted 1,2,4-triazole **3w** in moderate yield. The favorable result provided the possibility of further modification of amino acid derivatives.

The compatibility and generality of the present method were further explored by the utilization of a wide range of hydrazones (Scheme 2). First, the reaction proceeded successfully with respect

Scheme 2. Synthesis of 1,2,4-Triazoles from Different Hydrazones[a,b]



[a]Reaction conditions: hydrazone **1** (0.3 mmol), **2a** (0.9 mmol), I_2 (20 mol %), and TBHP (0.9 mmol) in CH_3CN (1 mL) under air at 90 °C for 4 h. [b]Isolated yield.

to hydrazones from diversely substituted aromatic aldehydes (**4a−k**). The orientation of substituents on the aromatic ring system had an obvious impact on the efficacy of the transformation (**4a−c**). It should be noted that hydrazones with a number of strong electron-withdrawing groups, including −CN, $-NO_2$, and $-CF_3$, were applicable under the standard conditions as well and the desired 1,2,4-triazole products were furnished in reasonable yields (**4i−k**). The naphthalene attached 1,2,4-triazole **4l** could be obtained in 72% yield. Furthermore, the hydrazone

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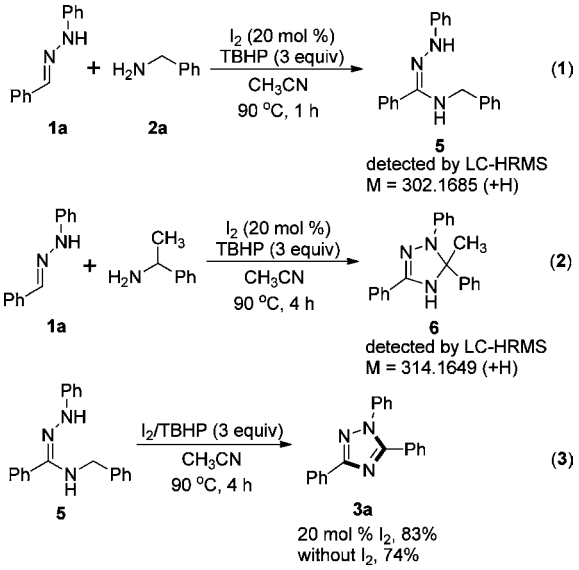
substrates with the furan and thiophene skeleton afforded the target heterocycles **4m** and **4n**, respectively, in 43% and 60% yields. The applicability of the transformation was further extended when hydrazones derived from numerous aliphatic aldehydes were subjected to the reaction, and moderate to excellent yields were observed (**4o**−**s**). More significantly, 3-styryl substituted 1,2,4-triazole **4t** could be produced by the employment of hydrazone from cinnamyl aldehyde as the reactant. We also prepared a series of hydrazone substrates from different aromatic or aliphatic hydrazines with benzaldehyde. To our delight, these hydrazone substrates participated in the reaction smoothly to afford the 1,2,4-triazole products in relatively lower to good yields (**4u**−**ad**). The structure of the obtained 1,3,5-trisubstituted 1,2,4-triazole **4d** was unambiguously confirmed by single X-ray diffraction analysis[13] (see the Supporting Information).

Preliminary mechanistic investigations indicated that a radical process was presumably involved in the reaction.[14] A series of control experiments were conducted as illustrated in Scheme 3 to

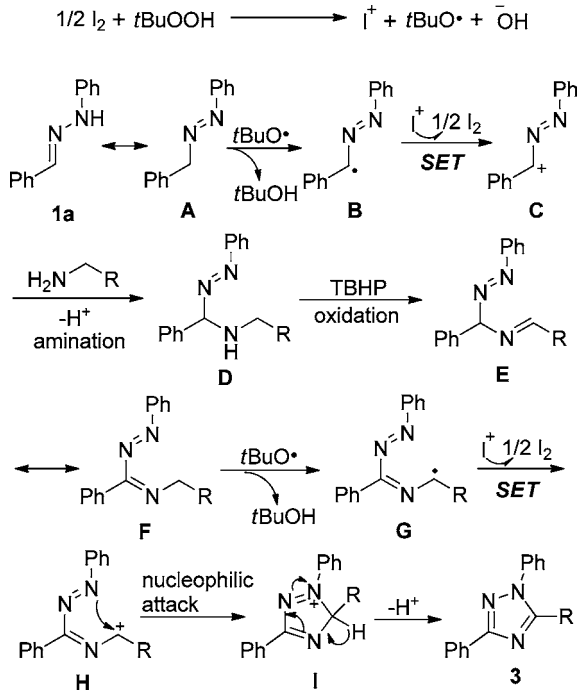
Scheme 3. Control Experiments



gain more insights into the mechanism. In the process of the standard reaction of **1a** and **2a**, the intermediate **5** was trapped by LC-HRMS (Scheme 3, eq 1). The reaction of substrate **1a** with α-methylbenzylamine was carried out under the standard conditions, and not surprisingly, the cyclized product **6** was detected by LC-HRMS (Scheme 3, eq 2). More significantly, we prepared the intermediate **5** and subjected it with 20 mol % I_2 and 3 equiv of TBHP or with only TBHP. Indeed, the final 1,2,4-triazole product **3a** was obtained in 83% or 74% yield, respectively (Scheme 3, eq 3). These mechanistic observations demonstrated the plausible intermediacy of **5**.

On the basis of the results from the preliminary mechanistic investigations and in previous reports,[11d,12a,b,15] a plausible reaction mechanism was proposed as shown in Scheme 4. Initially, **1a** underwent tautomerization via a 1,3-hydrogen shift to form diazo compound **A**, which was presumably involved in a hydrogen abstraction from benzylic C−H bond to generate a carbon radical **B**. In the presence of I^+ the oxidation of the radical **B** generated a benzylic cation **C** via a single-electron-transfer process.[15d] Intermediate **C** could be attacked by an amine through nucleophilic addition to provide **D**, which was regarded as the tautomer of compound **5** (Scheme 3, eq 1). An oxidative

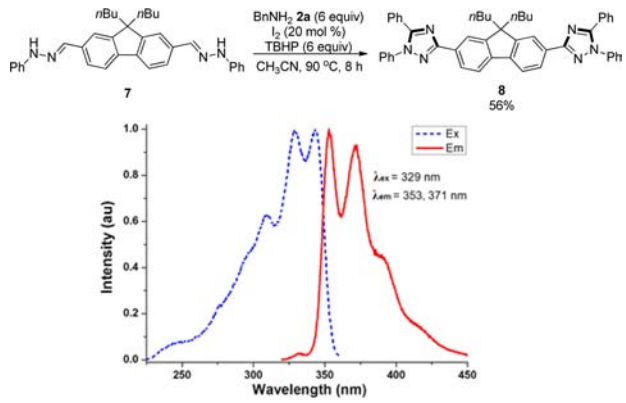
Scheme 4. Plausible Reaction Mechanism



dehydrogenation process in **D** led to intermediate **E**, which went through tautomerization to give **F**. Finally, **F** underwent a similar radical process to the previous pathway to give rise to intermediate **I**, which could be further converted to the final 1,2,4-triazole product **3** via the subsequent dehydrogenative aromatization process.[11d,15e] The I_2−I^+ redox process by promoting reductive cleavage of the O−O bond in the peroxide played a pivotal role in the C−N bond formations.[11d,12e]

Fluorene derivatives have been extensively investigated as notable optoelectronic materials for organic electronic devices due to their excellent fluorescent properties.[16] The synthetic utilization of our methodology is illustrated by the expedient synthesis of fluorene-triazole compound **8** as demonstrated in Scheme 5. The photophysical property of compound **8** was

Scheme 5. Synthetic Utilization of the Metal-Free Method



tested by fluorescence measurements. This result implied that the fluorene-triazole compound **8** had a potential application in the field of fluorescent material.

In conclusion, we have developed a highly attractive strategy for rapid and efficient construction, in a metal-free mediated intermolecular fashion, of molecules containing 1,2,4-triazole

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moieties from hydrazones and amines. The methodology features readily accessible starting reagents, general and convenient operating conditions, a broad substrate scope, and high efficiency. The reaction can be easily scaled up to gram scale, thereby providing the possibility for the scaled production of structurally diverse 1,2,4-triazoles. Further studies toward improving intensive understanding of the detailed reaction mechanism and extending the practical application of this methodology are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00277.

Experimental details, spectral and analytical data, copies of ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

Crystallographic data for **4d** (CIF)

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Notes

The authors declare no competing financial interest.

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(13) Compound **4d** was determined by X-ray crystallography. See the Supporting Information for full details. CCDC 1436037 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(14) The radical trapping experiments were conducted in the presence of radical scavengers. The yield of the reaction sharply decreased with the addition of TEMPO (2,2,6,6-Tetramethylpiperidine 1-oxyl) or BHT (2,4-di-*tert*-butyl-4-methylphenol) (see the Supporting Information).

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