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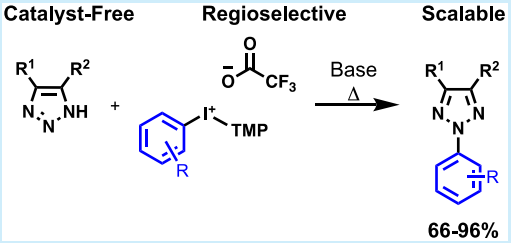
Catalyst-Free Regioselective N^2 Arylation of 1,2,3-Triazoles Using Diaryl Iodonium Salts

Sahar Roshandel, Maiko J. Lunn, Golam Rasul, Daniel Sylvinson Muthiah Ravinson, Suresh C. Suri, and G. K. Surya Prakash*

Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, California 90089-1661, United States

Supporting Information

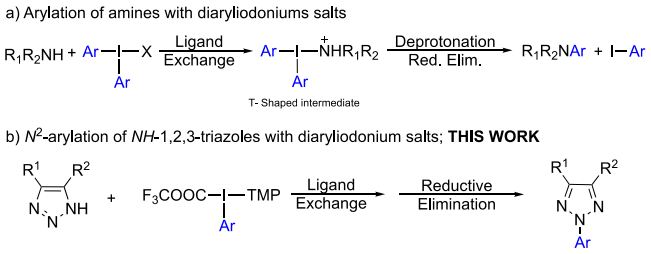
ABSTRACT: The widespread application of 1,2,3-triazoles in pharmaceuticals has resulted in substantial interest toward developing efficient postmodification methods. Whereas there are many postmodification methods available to obtain N^1-substituted 1,2,3-triazoles, developing a selective and convenient protocol to synthesize N^2-aryl-1,2,3-triazoles has been challenging. We report a catalyst-free and regioselective method to access N^2-aryl-1,2,3-triazoles in good to excellent yields (66−97%). This scalable postmodification protocol is effective for a wide range of substrates.



The extensive biological activities of 1,2,3-triazoles including anticancer, anti-inflammatory, and antibacterial characteristics have led to the frequent utilization of this scaffold in medicinal chemistry.[1] Regioselective copper-[2,3] and ruthenium-catalyzed[4] cycloaddition of azides and alkynes was reported in 2002 and 2007, giving easy access to 1,4- and 1,5-substituted 1,2,3-triazoles, respectively. Since then, many practical methods have been developed for the postmodification of 1,2,3-triazoles to provide N^1-substituted 1,2,3-triazoles.[5] On the contrary, only a few synthetic methods have been reported to access N^2-substituted 1,2,3-triazoles[6−10] despite their promising biological activities.[11−13] N^2-Aryl-1,2,3-triazole-containing molecules display interesting biological activities. For example, they have been used in a potent dual orexin receptor antagonist for the treatment of primary insomnia.[14] The simplest approach to access such N^2-substituted triazole motifs would be through the postmodification of readily available 1,2,3-triazoles. However, the existing postmodification methods that produce N^2-aryl-1,2,3-triazoles in a regioselective manner suffer significant drawbacks. For instance, the regioselectivity of the reaction can be controlled by using sterically hindering groups on the C4 and C5 positions of NH-1,2,3-triazoles.[15−19] Whereas such protocols are selective toward N^2 substitution, they unavoidably suffer from a limited substrate scope. The research groups of Shi[20] and Buchwald[21] have independently developed protocols that use Cu- and Pd-based catalysts, respectively, to conduct the arylation of NH-1,2,3-triazoles. Despite the high N^2 selectivity and wide substrate range of these methods, there are drawbacks, such as the cost and toxicity associated with the use of transition-metal catalysts. The presence of even traces of metal impurities in marketed drugs creates a significant challenge for using such catalysts in the pharmaceutical industry. Therefore, it is desirable to move toward developing regioselective metal-free methodologies to access such biologically valuable 1,2,3-triazole motifs with potential applications in the pharmaceutical industry.

Recently, the research groups of Olofsson[22] and Stuart[23] have reported the regiospecific N arylation of amines using diaryl iodonium salts, which eliminates the need to use toxic and expensive transition-metal catalysts to form a C−N bond (Scheme 1a). The reaction proceeds through the formation of a T-shaped intermediate, from which the desired N-arylated product is formed by reductive elimination. Inspired by their work, we wondered whether the diaryl iodonium salts can be utilized for the regioselective arylation of 1,2,3-triazoles, being particularly interested in N^2 substitution. Given that diaryl iodonium salts are bench-stable and can be easily synthesized from inexpensive reagents (iodoarenes or arenes), replacing conventional catalysts with these salts would provide a metal-free and cost-effective protocol to obtain N^2-aryl-1,2,3-triazoles.

Scheme 1. (a) Metal-Free Arylation of Amines with Diaryl Iodonium Salts by Stuart and Olofsson Research Groups and (b) N^2 Arylation of 1,2,3-Triazoles with Diaryl Iodonium Salts[a]



[a]TMP: 1,3,5-trimethoxyphenyl.

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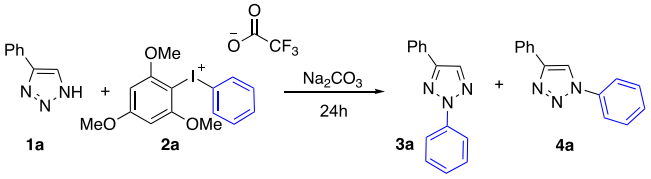
We started our investigation with 4-phenyl-1,2,3-triazole (**1a**) as the model substrate and phenyl(2,4,6-trimethoxyphenyl)-iodonium trifluoroacetate (**2a**) as the model diaryl iodonium salt. When **1a** (0.2 mmol; 1 equiv) was treated with **2a** (2 equiv) in the presence of sodium carbonate (1.2 equiv) in toluene for 24 h at 100 °C (Table 1, entry 1), the formation of N^1- and N^2-aryl-substituted triazoles was observed, along with 100% consumption of the starting substrate. Excitingly, we observed excellent regioselectivity toward the formation of the N^2-substituted triazole **3a** (N^2/N^1 = 89:11), which was isolated through chromatography in 85% yield.

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a 4a

entry	2a (equiv)	Na_2CO_3 (equiv)	T (°C)	solv	$\%X_{1a}$[b]	3a/4a[b]	$\%Y_{3a}$[c]
1	2	1.2	100	toluene	100	89:11	85
2	2	1.2	100	DMF	100	85:15	79
3	2	1.2	100	CH_3CN	100	64:36	56
4	2	1.2	100	dioxane	100	83:17	78
5	2	1.2	75	toluene	92	81:19	75
6	2	1.2	50	toluene	84	68:32	62
7	2	1.2	25	toluene	80	68:32	61
8	1.6	1.2	100	toluene	100	92:8	88
9	**1.2**	**1.2**	**100**	**toluene**	**100**	**95:5**	**94**
10	1.2	0.6	100	toluene	100	85:15	82
11	1.2	0	100	toluene	70	56:44	45

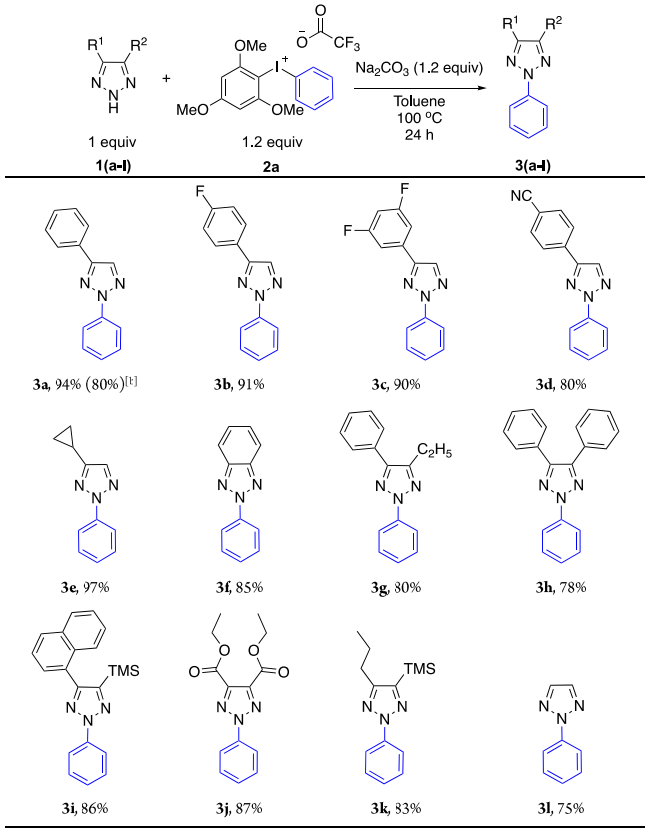
[a]0.2 mmol **1a** was treated with the indicated amount of **2a** and Na_2CO_3 in 2 mL of anhydrous and degassed solvent under argon. **1a** and **2a** were prepared according to the previously reported procedures by our group[24] and Stuart's group,[25] respectively. [b]% conversion of **1a** and ratio of **3a** to **4a** were determined by GC–MS. [c]Isolated yield of **3a**.

Obtaining such high regioselectivity without the use of any metal catalyst and directing groups is unprecedented, and it encouraged us to further explore the optimum reaction conditions to produce N^2-aryl-1,2,3-triazoles with even higher selectivity. When we changed the reaction solvent from toluene to other more polar solvents, such as DMF, CH_3CN, or dioxane, a decrease in the regioselectivity of the reaction was observed (Table 1, entries 1–4). Reducing the reaction temperature to 75, 50, and 25 °C also had an adverse impact on both the conversion and the selectivity of the reaction (Table 1, entries 5–7). Whereas poor N^2 selectivity was still observed at lower temperatures, our results showed that heating is crucial for achieving a high regioselectivity.

Decreasing the **2a** amount during the reaction from 1.6 equiv to 1.4 equiv increased the selectivity for **2a** to 95%, along with 94% isolated yield. With regards to sodium carbonate, a decrease in its amount from 1.2 to 0.6 equiv decreased the **3a** selectivity, whereas **2a** conversion still remained 100%. Finally, the reaction also proceeded in the absence of any Na_2CO_3 base additive. However, after 24 h, only 70% **1a** conversion was observed. Also, the selectivity of the reaction to produce **3a** decreased significantly (**3a**/**4a** 56:44) in the absence of Na_2CO_3.

With the optimized conditions in hand providing 94% of the desired N^2 product (Table 1, entry 9), we investigated the efficacy of this reaction for various NH-1,2,3-triazoles. Initially, the reaction efficacy for various C4-substituted 1,2,3-triazoles (Schemes 2, 3a–e) was tested to explore the effect of C4 substitution on the regioselectivity of the reaction. Interestingly, the reaction proceeded with excellent N^2 regioselectivity for all C4-substituted substrates, regardless of their electronic nature. Furthermore, the cyano group (**3d**) as well as the cyclopropyl group (**3e**) was well tolerated under the reaction conditions, and isolated yields of 80 and 97% were obtained for their corresponding products, respectively. Next, we explored the effect of both C4 and C5 disubstitution on the regioselectivity and yield of the reaction. Towards this endeavor, disubstituted 1,2,3-triazoles were reacted with **2a** under the reaction conditions.

Scheme 2. Substrate Scope of Regioselective N^2 Arylation of Various NH-1,2,3-Triazoles Using 2a[a]



[a]0.2 mmol **1**, 0.24 mmol **2a**, and 0.24 mmol sodium carbonate in 2 mL of anhydrous and degassed toluene under argon. [b]Reaction was conducted on a 2 mmol scale.

Initially, we screened benzotriazole because the previously reported N^2 arylation methods were not successful in obtaining any regioselectivity with benzotriazole as the substrate.[20,21] However, with our protocol, we observed high N^2 selectivity and obtained the corresponding N^2 product (**3f**) in 85% yield. This is particularly exciting because N-substituted benzotriazoles are highly sought-after moieties in pharmaceuticals,[26,27] and, to the best of our knowledge, this is the only protocol that provides easy access to N^2-aryl-benzotriazole in a regioselective manner. Among other disubstituted triazoles, both 4-ethyl-5-phenyl and

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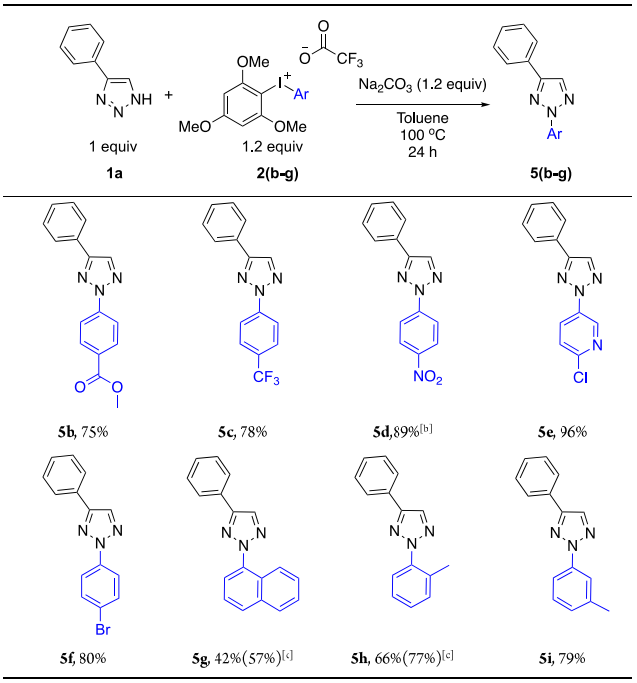
Scheme 3. Substrate Scope of Regioselective N^2 Arylation of 1a Using Various Diaryl Iodonium Salts[a]



[a]0.2 mmol **1a**, 0.24 mmol **2**, and 0.24 mmol sodium carbonate in 2 mL of anhydrous and degassed toluene under argon. [b]Reaction was conducted at 65 °C because at higher temperatures decomposition of the corresponding diaryl iodonium salt was observed. [c]Yields reported in parentheses are obtained at 120 °C.

4,5-diphenyl triazole were arylated at the N^2 position with high selectivity, and 80 and 78% of their corresponding products were isolated, respectively. Subsequently, triazole containing sterically hindering moieties on both C4 and C5 (trimethylsilyl and naphthyl groups, respectively) was subjected to the reaction conditions. We discovered that the reaction performed well in all cases (**3(g−i,k)**), and high N^2 selectivity was obtained regardless of the steric bulk of the substituents. The ester moiety was also well tolerated under the reaction conditions and afforded the corresponding product **3j** in 87% yield. Thus it seems that the substitution in the four and five positions of the triazole does not significantly influence the yield and selectivity of reaction. In the case of NH-1,2,3-triazole, without any substitution on the triazole ring, the reaction proceeded slower as compared with **1a**, and 79% **1l** conversion was achieved after 24 h. Nonetheless, the reaction was highly N^2-selective, similar to the other substrates (isolated yield 75%). This proves that the N^2 selectivity is not directed by the steric hindrance of C4 or C5 substitutions. Rather, it is more likely that the N^2-substituted product is thermodynamically favorable compared with the N^1-substituted product, as will be evident from the results of our density functional theory (DFT) calculations presented vide infra. Finally, the scalability of this protocol was investigated with substrate **1a** on a 2 mmol scale. The reaction performed well on the higher scale and afforded the corresponding N^2 product (**3a**) in 80% yield.

Subsequently, we investigated the effect of different diaryl iodonium salts on the reaction efficiency and selectivity using **1a** as the model triazole substrate (Scheme 3). The reaction proceeded with high selectivity with diaryl iodonium salts containing deactivating moieties such as −COOR, $-CF_3$, and $-NO_2$ in the para position, affording the corresponding N^2 products **5(b−d)** in high yield (75, 78, and 89%, respectively). In the case of **5d**, with *p*-NO_2 substitution, the reaction was conducted at 65 °C because we observed the decomposition of the diaryl iodonium salt at elevated temperatures. We also found that this reaction proceeds smoothly with diaryl iodonium salts containing mildly activating moieties such as $-CH_3$ (**5i**). Apart from the phenyl ring, the pyridinyl ring can also be used for this arylation because product **5e** was obtained in high N^2 selectivity and excellent yield. Thus 4-substitutions in the iodonium salt aryl ring and the presence of a heterocycle do not inhibit the reaction or alter the product selectivity to a significant degree. On the contrary, the selectivity was drastically influenced by ortho substitutions on the aryl ring, as in the case of **2g**, we observed an almost 1:1 ratio of N^1 and N^2 products. The lack of selectivity is presumably due to the steric hindrance of ortho substituents on the aryl group. To further examine the effect of ortho substitution on the selectivity, **2h** and **2i** with *o*-Me and *m*-Me groups, respectively, were exposed to the reaction conditions. As anticipated, the *ortho*-methyl-substituted **2h** offered poor N^2 selectivity, whereas the *meta*-methyl-substituted **2i** afforded the corresponding N^2 product (**5i**) with high selectivity.

To gain a better insight into the reaction mechanism and the reason for the N^2 regioselectivity of the reaction, we conducted DFT calculation studies of the plausible intermediates and transition states. On the basis of our findings, we postulate that the regioselective N^2 arylation of 1,2,3-triazoles proceeds through a ligand-exchange, process followed by reductive elimination to furnish the thermodynamically favored N^2-aryl-1,2,3-triazole. During the initial ligand-exchange process, the CF_3COO^- ligand coordinated to the iodine center is replaced by the triazole moiety. The triazole can coordinate to the iodine in two possible ways: through N^1 (I_B; on right) or N^2 coordination (I_A; on left) (Scheme 4). The relative energies of the two competing routes (I and II) based on the DFT calculations are shown in Scheme 4a. According to our calculations, the I_A intermediate is 2.86 kcal/mol more stable than the I_B intermediate. This energy difference indicates that at any time the concentration of I_A is slightly more than that of I_B in the reaction mixture. The comparison of relative energies of transition states ($\Delta\Delta G^{\ddagger}$ = 0.22 kcal/mol) illustrates that the formation of N^1 product is kinetically favored, as we observed during the reaction optimization process. However, when the relative energy of the N^2 products (A + C) is compared with that of the N^1 products (B + C), the former is significantly (by 4.96 kcal/mol) more stable (Scheme 2a). These calculations demonstrate that the formation of N^2 product is thermodynamically favored. As a result, the arylation protocol gives the N^2-substituted products with high selectivity at higher temperatures. Similarly, in the case of ortho-substituted aryls, where we observed poor N^2 selectivity, our calculation shows that N^1 product and N^2 product are, respectively, kinetically and thermodynamically favored (Scheme 4b). To get thermodynamic control, we conducted the reactions at 120 °C and, indeed, the N^2 selectivity (**5g** and **5h**) increased at elevated temperatures, and we were able to obtain the N^2 products in 57 and 77% yield, respectively.

In conclusion, we have successfully developed a scalable, transition-metal/catalyst-free methodology that provides easy access to N^2-aryl-1,2,3-triazoles in a highly regioselective manner. Moreover, this postmodification method arguably presents a cost-effective protocol to synthesize N^2-aryl-1,2,3-

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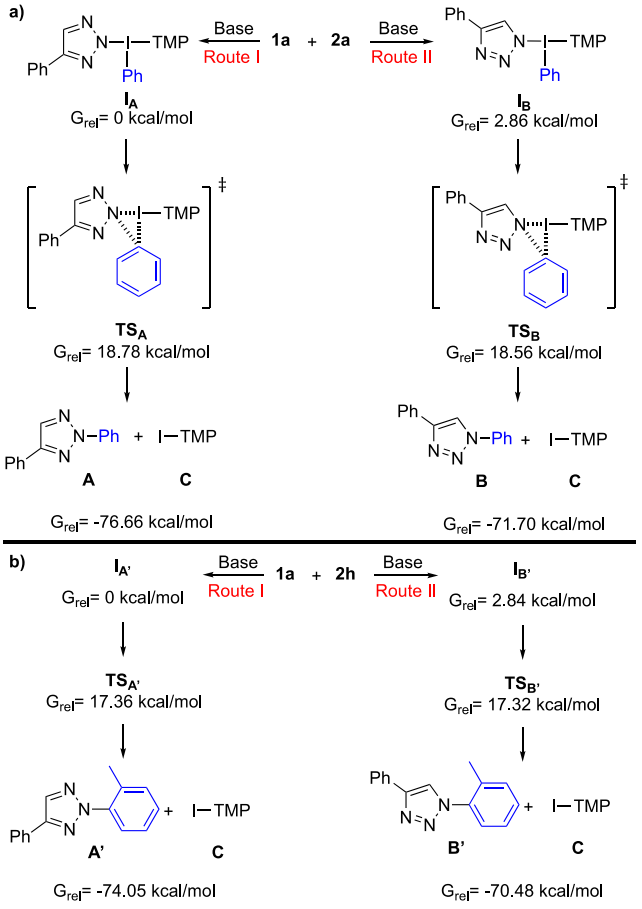
Scheme 4. (a) Plausible Reaction Mechanism of N^2 Arylation of 1,2,3-Triazoles with DFT Calculations of the Potential Intermediates and Transition States and (b) DFT Calculations of the Potential Intermediates and Transition States for the ortho-Substituted Aryls[a]



[a]TMP: 1,3,5-trimethoxyphenyl.

triazoles because it moves away from the use of costly and toxic transition-metal catalysts. Additionally, the isolable byproduct of the reaction, iodo-2,4,6-trimethoxybenzene, can be recycled to synthesize back the diaryl iodonium salts. Therefore, we believe that the work presented here provides a convenient and green method to furnish biologically valuable N^2-aryl-1,2,3-triazoles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02140.

Experimental procedures, NMR spectra, and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gprakash@usc.edu (G.K.S.P.).

ORCID

G. K. Surya Prakash: 0000-0002-6350-8325

Notes

The authors declare no competing financial interest.

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