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1,6-Addition of 1,2,3-NH triazoles to *para*-quinone methides: Facile access to highly selective N^1 and N^2 substituted triazoles†

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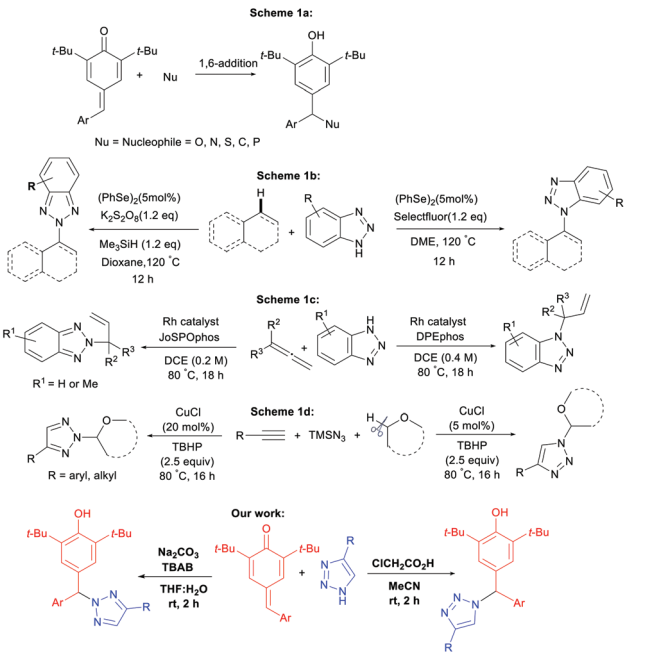
The regioselective syntheses of N^1 and N^2 substituted triazoles through a 1,6-addition reaction of 1,2,3-NH triazoles to *p*-quinone methide were achieved under mild reaction conditions. The present reactions showed superior results in terms of selectivity, mild reaction conditions, short reaction time and broad substrate scope with good functional-group compatibility. Considering the high synthetic value of N^1- and N^2-substituted compounds and *p*-QM related research, the present strategy will greatly benefit researchers in various fields.

Since the development of *p*-quinone methides (*p*-QMs) as valuable Michael acceptors, these compounds have received massive attention from chemists for the annulations[1] and variety of nucleophilic 1,6-addition reactions employing acids,[2] bases,[3] metal catalysts[4] or other catalysts (Scheme 1a).[5] Moreover, such addition reactions to *p*-QMs are characteristic of step and atom economy. Recently, some reviews[6] emphasized the synthesis of structurally diverse molecules through 1,6-additions and annulation reactions of *p*-QMs. Similarly, *p*-QMs proved to be suitable precursors to construct a wide range of 2,4,6-trisubstituted phenols and substituted triarylmethane derivatives. Particularly, heterocyclic triaryl methane molecules have shown diverse biological applications.[7]

Among a variety of heterocyclic systems, N-substituted 1,2,3-triazoles and their derivatives have exhibited tremendous applications in the fields of biological science,[8] material chemistry,[9] medicinal chemistry,[10] synthetic organic chemistry[11] and other fields.[12] It is seen in the literature that, both N^1 and N^2 functionalized triazoles[13] have shown different properties[14] and even totally opposite properties[15] in some cases. Due to this uniqueness of N-substituted triazoles, their synthesis has attracted a wide by variety of research groups. Thus, the growing research in this area has led to a strong desire for the effective syntheses of substituted triazoles, especially those that provide good regio-selectivity. It is well known that the synthesis of regioselective N^2 over N^1 functionalization is challenging.[16] Most of the synthetic routes provide N^1 functionalized triazole products.[17] However, several methods have also been reported for the synthesis of N^2-substituted molecules[18] employing metal catalysts[19] and metal free conditions.[20] Nevertheless, the attempts in improving N^1 and N^2 regioselectivity in triazoles for identical functionalizations have found very limited success. The research groups of B. Zhang



Scheme 1 Regioselective N^1 and N^2 functionalization of 1,2,3-triazoles.

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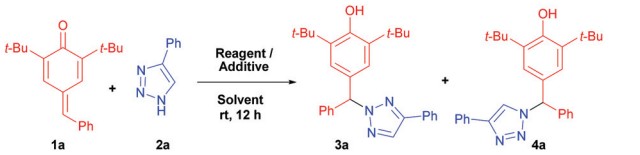
and K. Sun reported organoselenium-catalyzed N^1- and N^2-selective aza-Wacker reactions of triazoles by carrying out the coupling of benzotriazoles with alkenes[21] at elevated temperatures for 12 h (Scheme 1b). In 2014, B. Breit's[22] group developed Rh(I)-DPEphos/JoSPOphos catalyzed N^1- and N^2-selective coupling of benzotriazoles with allenes. The authors did these coupling reactions under thermal conditions for 18 h (Scheme 1c). Recently, the research groups of Zhao and Wei disclosed the copper-catalyzed three-component reaction of alkynes, $TMSN_3$ and ethers for the synthesis of N^1- and N^2-oxyalkylated 1,2,3-triazoles.[23] The authors carried out these reactions under thermal conditions for 16 h (Scheme 1d). Despite the progress made towards the regioselective synthesis of N^2-substituted triazoles, these strategies suffer from significant limitations. For examples, regioselectivity is highly controlled by the bulky groups at the C4 and C5 positions of triazoles,[24] the reaction conditions are harsh, reaction times are long[25] and toxic and expensive metal catalysts are used.[22] Thus, the development of protocols for the regioselective synthesis of N^1- and N^2-substituted 1,2,3-triazoles using readily available starting materials under environmentally benign conditions is still desirable. In this context, we envisaged that the coupling of *p*-QMs and 1,2,3-triazoles; the two biologically important precursors, would furnish new interesting structural features, which would be potential candidates with some desired pharmacological activity. Additionally, to the best of our knowledge, there is no literature report on the 1,6-addition of triazoles to *p*-QMs to date. In a continuation of our research towards developing new methodologies for the synthesis of functionalized organic molecules,[26] we herein presenting an unprecedented highly regio-selective synthesis of N^1- and N^2-functionalized triazoles through the 1,6-addition of triazoles to *p*-QMs.

The initial experiments were directed towards identifying the optimized reaction conditions by employing *p*-QM (**1a**) and 1,2,3-triazole (**2a**) under various reaction conditions and the results are summarized in Table 1. The reactions of **1a** with **2a** in the presence of methanesulfonic acid in acetonitrile at room temperature gave N^1-functionalized triazole **3a** and N^2-functionalized triazole **4a** products in 38% and 50% yields respectively (Table 1, entry 1). Subsequently, a series of Brønsted acids were examined in acetonitrile to improve the yield and selectivity (Table 1, entries 2–8). Among them, chloroacetic acid was found to be the best and showed very good regio-selectively in affording triazole **4a** as the major product and **3a** as the minor product with 78% and 18% yields respectively (Table 1, entry 3). Similarly, several Lewis acids were also examined for the present addition reactions in acetonitrile. However, the regio-selectivity was not fruitful and yields of products were also moderate (Table 1, entries 9–14). We then explored the effect of different solvents for the present study using chloroacetic acid as the reagent. Accordingly, reactions in polar solvents, such as DMF and MeOH, did not proceed. Very low yields & selectivity were observed in these reactions (Table 1, entries 15 and 16). Reactions in relatively less polar solvents, like DCM, THF and Toluene proceeded moderately in terms of yields and the regio-selectivity was very low (Table 1, entries 17–19). We then turned our attention towards using basic reagents. Reactions of **1a** and **2a** using organic bases like DABCO, DBU and Et_3N produced the isomeric products in moderate to low yields and low selectivity (Table 1, entries 20–22).

Subsequent reactions using K_2CO_3 and Na_2CO_3 in aqueous acetonitrile (1 : 1) produced interesting results. Although the yields were low, the regio-selectivity was reversed, *i.e.* product **3a** was observed as the major and **4a** as the minor product (Table 1, entries 23 and 24).

The above two reactions encouraged us to optimize the reaction conditions further. NaOAc was found to be inefficient for the present regioselectivity and the products obtained in very low yields (Table 1, entry 25). Subsequently, we performed several reactions in aq. organic solvents (1 : 1) using Na_2CO_3 as the base and TBAB as an additive (Table 1, entries 26–29). We

Table 1 Optimization studies towards 1,6 addition reaction of 1,2,3 triazole to *p*-QM[a]



1a 2a 3a 4a

Entry	Reagent (1 equiv.)	Additive (0.3 equiv.)	Solvent	**3a** [b] (%)	**4a** [b] (%)
1	MsOH	—	MeCN	38	50
2	AcOH	—	MeCN	NR	41
3	**$ClCH_2CO_2H$**	—	**MeCN**	**18**	**78**
4	Cl_3CCO_2H	—	MeCN	30	56
5	TFA	—	MeCN	20	40
6	PTSA	—	MeCN	31	40
7	Anisic acid[c]	—	MeCN	NR	NR
8	Benzoic acid[c]	—	MeCN	NR	NR
9	$Cu(OAc)_2$	—	MeCN	09	14
10	$Cu(OTf)_2$	—	MeCN	25	55
11	$CuCl_2$	—	MeCN	36	57
12	$AlCl_3$	—	MeCN	44	46
13	$FeCl_3$	—	MeCN	20	62
14	$BF_3(OEt)_2$	—	MeCN	15	63
15	$ClCH_2CO_2H$	—	DMF	NR	20
16	$ClCH_2CO_2H$	—	MeOH	12	35
17	$ClCH_2CO_2H$	—	DCM	14	28
18	$ClCH_2CO_2H$	—	THF	16	53
19	$ClCH_2CO_2H$	—	Toluene	26	22
20	DABCO	—	MeCN	30	42
21	DBU	—	MeCN	30	38
22	Et_3N[c]	—	MeCN	Trace	Trace
23	K_2CO_3	—	THF-H_2O	42	15
24	Na_2CO_3	—	THF-H_2O	62	15
25	NaOAc	—	THF-H_2O	06	10
26	**Na_2CO_3**	**TBAB**	**THF-H_2O**	**74**	**16**
27	Na_2CO_3	TBAB	DCM-H_2O	45	40
28	Na_2CO_3	TBAB	MeCN-H_2O	45	38
29	Na_2CO_3	TBAB	AcOH-H_2O	NR	12
30[d]	Na_2CO_3	TBAB	THF-H_2O	48	32

[a] All the reactions were carried out using **1a** (1 equiv., 0.339 mmol) and **2a** (1 equiv., 0.339 mmol) at room temperature. [b] Isolated yields. [c] Products were formed in very low yields and more than 90% starting materials were isolated back. [d] Reaction carried out at 50 °C.

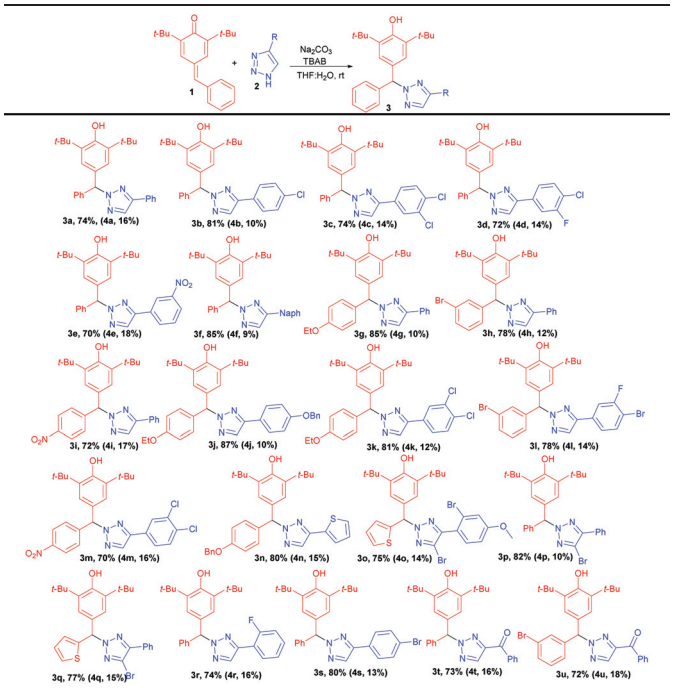
were delighted to see both regioselectivity and yields were enhanced when the reaction was carried out in aq. THF (Table 1, entry 26). The regioselectivity was dropped when the above reaction was performed at a slightly higher temperature (Table 1, entry 30).

Under the optimal reaction conditions, initially we investigated the substrate scope for the synthesis of various N^2 substituted triazoles and the results are tabulated in Table 2. Halogen substituted phenyl 1,2,3-triazoles reacted well with **1a** affording the desired products **3b–3d** in good yields. Triazole with a strong electron withdrawing group ($-NO_2$) also reacted smoothly to furnish the product **3e** with good yield. Similarly, naphthyl substituted triazole afforded the corresponding product **3f** in very good yield. Next, we explored the reactivity of substituted *p*-QMs under the optimized conditions. Accordingly, OEt, Br and NO_2 substituted substrates reacted well with 4-phenyl-1,2,3-triazole (**2a**) to furnish the desired products **3g–3i** in very good yields. Furthermore, we also used differently substituted starting materials for the present study. Thus, several substituted **1a** and **2a** molecules underwent smooth 1,6 addition reactions and furnished the corresponding products **3j** to **3u** with good yields.

On the other hand, various N^1 substituted triazoles were also synthesized under the optimized conditions and the results are summarized in Table 3. Triazoles with halogen substitution reacted with **1a** to afford the desired products **4b–4d** in 72–81% yields. Notably, a strong electron withdrawing nitro group also underwent a smooth reaction and led to the formation of **4e** in a good yield. Similarly, *p*-QM also showed good functional group tolerance under the present reaction conditions and produced the desired products **4f–4i** with good yields. Apart from this, both **1a** and **2a** with different substitutions also reacted smoothly and the corresponding products **4j–4n** were obtained in good yields.

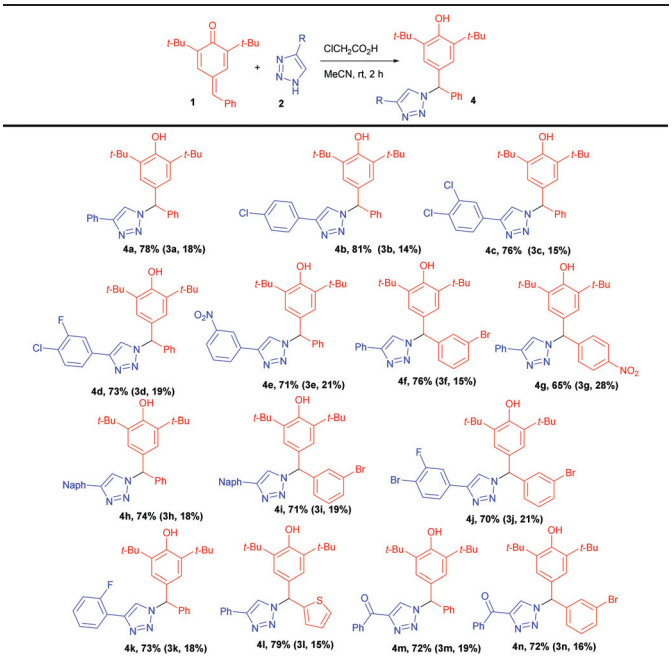
We also extended this protocol to other aza-heterocyclic compounds, such as isatin and morpholine. We got the corresponding 1,6-addition products **6a** and **6b** with very good yields (Scheme 2).

Table 2 Preparation of N^2 substituted triazoles[a]

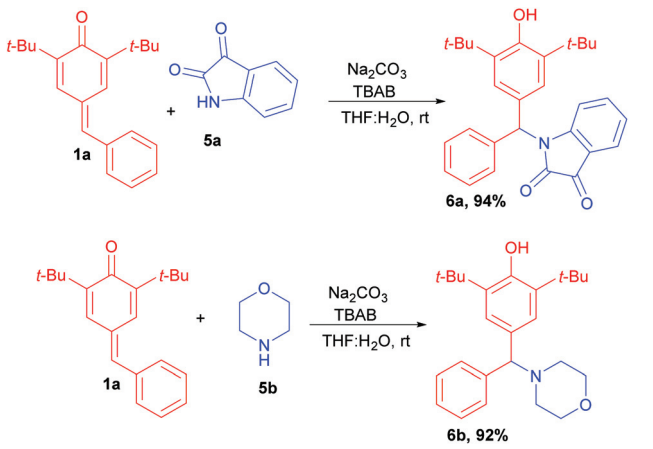


[a] Reaction conditions: **1** (1 equiv., 0.339 mmol), **2** (1 equiv., 0.339 mmol), Na_2CO_3 (1 equiv., 0339 mmol) and TBAB (0.2 equiv., 0.067 mmol) in THF : H_2O (1 : 1, 2.0 mL) at room temperature for 2 h. Yields in the parenthesis are of the corresponding minor isomers.

Table 3 Preparation of N^1 substituted triazoles[a]



[a] Reaction conditions: **1** (1 equiv., 0.339 mmol), **2** (1 equiv., 0.339 mmol) and $ClCH_2CO_2H$ (1 equiv., 0339 mmol) in MeCN (2.0 mL) at room temperature for 2 h. Yields in the parenthesis are of the corresponding minor isomers.



Scheme 2 1,6-Addition of isatin and morpholine to *p*-QM.

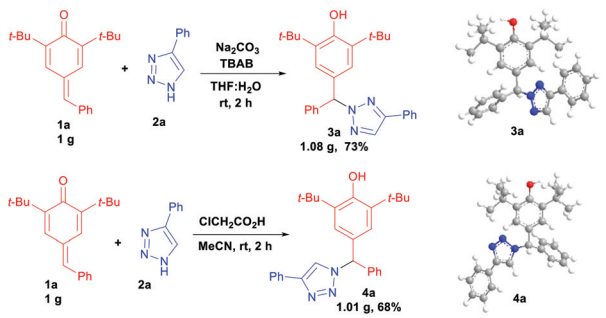
To examine the scale up feasibility of the present reactions, we performed reactions using a 1 g quantity of starting material **1a** under the standard conditions. We selected **1a** and **2a** to react under both the optimized reaction conditions. To our delight, the yield of the corresponding products remained reasonable, with 73% of **3a** and 68% of **4a**.

We also performed crystallization of both regioselective products. Interestingly, structures of both products **3a** and **4a** were confirmed by X-ray single crystal analysis (diffraction analysis) and the corresponding crystal structures are shown in Scheme 3 (CCDC 2103494 and 2103495†).

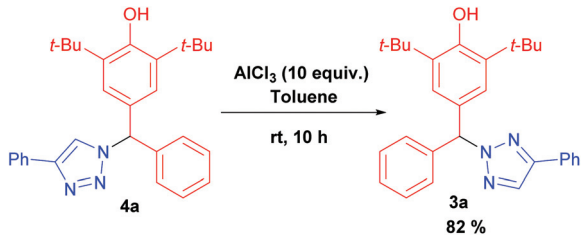
As per a literature report,[2a] we attempted to remove the *t*-butyl group from the product using an excess amount of $AlCl_3$. However, to our surprise, N^1 substituted triazole **4a** was isomerized into N^2 substituted triazole **3a** when treated with an excess amount of $AlCl_3$ in toluene at room temperature with 82% yield (Scheme 4). Interestingly, such an isomerization is known for N^2 to N^1 substituted triazole[27] using catalytic Zn $(OTf)_2$ but not the reverse. We expect such isomerization might be proceeding *via* a retro aza-Michael addition reaction.

In order to understand the reaction mechanism, we performed a few control experiments and the results are depicted in Scheme 5. When we used *N*-methyl triazole (**2a′**), the reaction did not proceed, which indicates the important role of the N–H moiety. Similarly, when reactions were performed in the absence of base and acid under the optimized reaction conditions, the corresponding products were not formed. Both the starting materials were isolated unaffected (Scheme 5c).

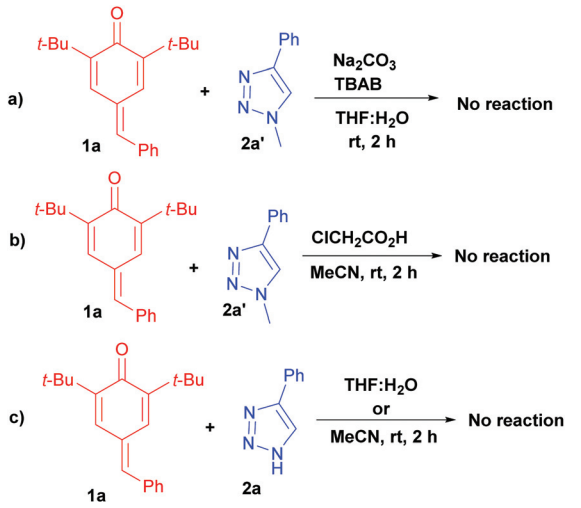
Based on the control experimental results and previous reports,[25] tentative mechanisms for 1,6 additions of 1,2,3-NH triazoles to *p*-QM are shown in Scheme 6. In the base mediated



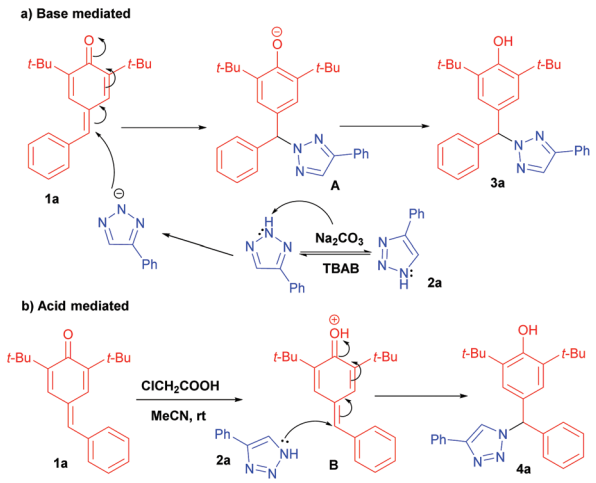
Scheme 3 Large scale reactions.



Scheme 4 Conversion of N^1 to N^2 substituted triazole.



Scheme 5 Control experiments.



Scheme 6 Tentative reaction mechanism.

reaction, deprotonation of the triazole in the presence of base forms the stable N^2 anion. Nucleophilic attack of the N^2 anion of triazole to *p*-QM **1a** leads to the formation of **A**. Subsequently, **A** under the reaction conditions converts into the desired N^2 substituted product **3a**. In the acid mediated reaction, *p*-QM **1a** undergoes protonation in the presence of chloroacetic acid to give **B**. The N^1 atom of 1,2,3-NH triazole **2a** acts as a nucleophile and attacks the protonated form of *p*-QM (**B**) to produce N^1 substituted product **4a** under the reaction conditions.

We have successfully demonstrated practical protocols towards the regioselective synthesis of N^1 and N^2 substituted triazoles *via* 1,6 addition reactions with *p*-QMs under mild reaction conditions. The present reactions showed superior results in terms of selectivity, reaction time, good functional-group compatibility and broad substrate scope. Interestingly, isomerization of the N^1 to N^2 substituted product was also studied employing $AlCl_3$. Investigations on the asymmetric

transformations and similar regioselective functionalizations are currently underway in our laboratory. Additionally, considering the extremely fast growth of 1,2,3-NH triazole and *p*-QM related research, we believe our strategy will greatly benefit researchers in various field.

Conflicts of interest

There are no conflicts of interest.

Acknowledgements

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