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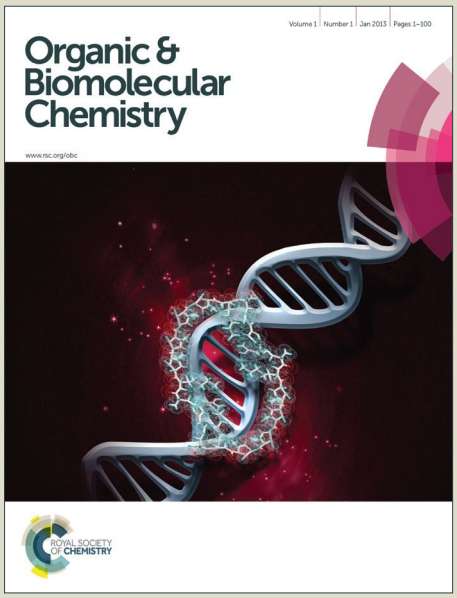

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COMMUNICATION

I_2–TBHP-catalyzed one-pot highly efficient synthesis of 4,3-fused 1,2,4-triazoles from *N*-tosylhydrazones and aromatic *N*-heterocycles *via* intermolecular formal 1,3-dipolar cycloaddition†

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Surendra Babu Inturi,[a,b] Biswajit Kalita*[a] and A. Jafar Ahamed*[b]

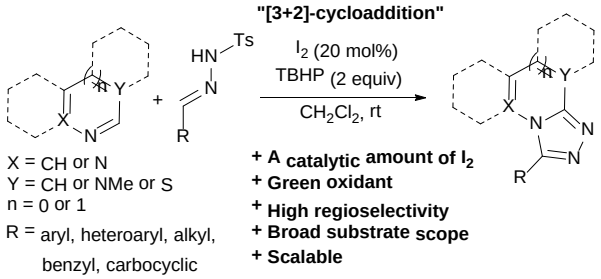
I_2–TBHP-catalyzed azomethine imine generation and its regioselective 1,3-dipolar cycloaddition (DC) reaction with aromatic *N*-heterocycles is developed to afford various 4,3-fused 1,2,4-triazoles in excellent yields. The method is operationally simple and highly efficient with broad functional group tolerability.

The [1,2,4]triazolo[4,3-*a*]pyridine and related 4,3-fused 1,2,4-triazoles constitute one of the most important structural templates present in a variety of molecules with biological importances. Many novel examples of this class of compounds have been demonstrated in multiple therapeutic areas and target classes.[1–3] Because of their importances and usefulness, construction of 4,3-fused 1,2,4-triazoles have attracted interest of synthetic organic and medicinal chemists for several years and hence development of efficient synthetic strategies to construct this motif is highly desirable.

Several methods have been devised to synthesize 4,3-fused 1,2,4-triazoles systems over the years. These methods in general involve palladium catalyzed reactions of 2-halopyridines with aryl hydrazides[4] or aryl hydrazines[5] to generate 2-pyridylhydrazides or 2-pyridylhydrazones respectively which are then converted to the triazolopyridines by a thermal[6] or an oxidative cyclization[7] reaction. Another approach involves conversion of 2-halopyridines to 2-pyridylhydrazines by S_NAr or a palladium catalyzed coupling reaction. This was then converted to triazolopyridines by a CDI mediated tandem reaction with appropriate carboxylic acids.[8] The triazolopyridines have also been successfully synthesized from the 2-pyridylhydrazines by reactions with carboxylic acids[9] or aldehydes[7] to synthesize 2-pyridylhydrazides or 2-pyridylhydrazones respectively followed by their cyclizations. These methods, although diverse, involve a multi-step synthesis process. Moreover, despite being successful, the transition metal catalyzed methods impose a general limitation to substrate scopes particularly with aryl halides.

In 2010, Maiti *et al.* reported iodosobenzene (PhIO) mediated reaction between *N*-tosylhydrazones and *N*-heterocycles to synthesize fused triazoles.[10] However, this method needed super-stoichiometric amount of PhIO (2 equiv) which is highly hazardous and explosive, and was applied only to a limited set of *para*-substituted pyridine and unsubstituted quinoline substrates. This led us to investigate a robust methodology as economically and ecologically benign alternative to the existing methods to synthesize this class of fused triazoles with broad substrate scope.

Within the context of non-metal based catalysts, readily available molecular iodine has enabled a significant development by virtue of its ability to generate reactive iodine species with diverse redox potential.[11–12] In continuation to our efforts in developing metal free methodologies,[13] we sought to develop a catalytic method for the synthesis of 4,3-fused 1,2,4-triazoles. Toward this approach we chose to use molecular iodine as a catalyst in presence of TBHP to generate azomethine imine ylides from a variety of *N*-tosylhydrazones and their regioselective intermolecular formal [3+2]-cycloaddition with aromatic *N*-heterocycles, which to best of our knowledge has never been reported (Scheme 1).



Scheme 1 I_2–TBHP-catalyzed synthesis of 4,3-fused 1,2,4-triazoles.

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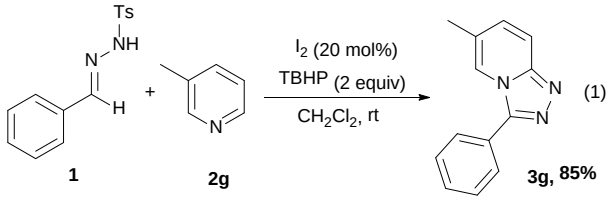
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

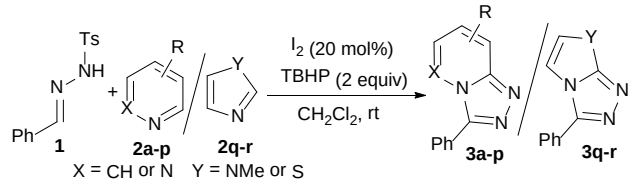
A thorough optimization of the reaction conditions,[14] the optimized catalytic system was established as: **1** (1 equiv), **2g** (2 equiv), I_2 (20 mol%), *tert*-Butyl hydroperoxide [TBHP (5–6 M) in decane] (2 equiv) in DCM at room temperature. The desired product **3g** was achieved in 85% yield with complete regioselectivity shown in eqn (1).



1 **2g** **3g, 85%**

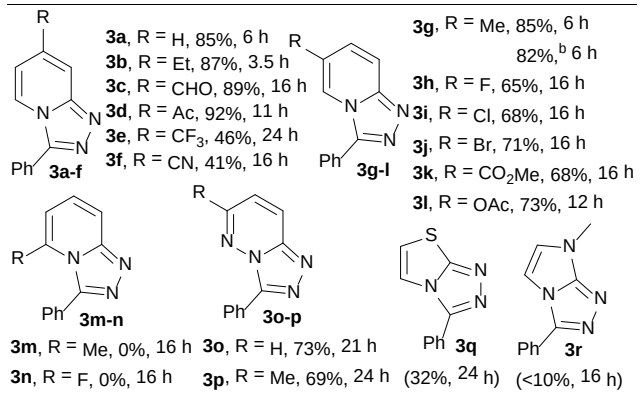
With the optimized condition in hand, we decided to evaluate the scope of the reagent system with various aromatic *N*-heterocycles. As shown in Table 1, it was evident that the in-situ formed azomethine amine ylide reactivity varied based on the substituents on the *N*-heteroaryls. It was found that aldehyde, ketone, ester, halogen and cyano groups were tolerated under the reaction conditions which can be utilized for further modifications. Strong electron withdrawing groups (EWG, $-CF_3$ and -CN) gave relatively low to moderate yields (Table 1, **3e–f**) while the electron donating groups (EDG, Me and Et) and halogen substituted substrates (**2h–j**) could react smoothly to offer the desired products in higher yields. It is noteworthy to mention that in case of the *meta* substituted pyridine substrates (**2g–l**), the 1,3-DC happened in a complete regioselective way as confirmed by single crystal X-ray diffraction analysis of **3h**.[15] Surprisingly, the reaction did not proceed at all with the *ortho* substituted pyridine derivatives (**3m–n**). It was interesting to note that the pyridazine substrates (**2o–p**) were very well tolerated under the reaction condition; whereas 5-membered heterocycles (**2q–r**) could react only moderately to afford the desired products in low yields. The catalytic transformation performed in 1 g scale with **1** was reproducible and yielded 82% of **3g**.

Table 1 The substrate scope of aromatic *N*-heterocycles[a]



1 **2a-p** **2q-r** **3a-p** **3q-r**

X = CH or N Y = NMe or S



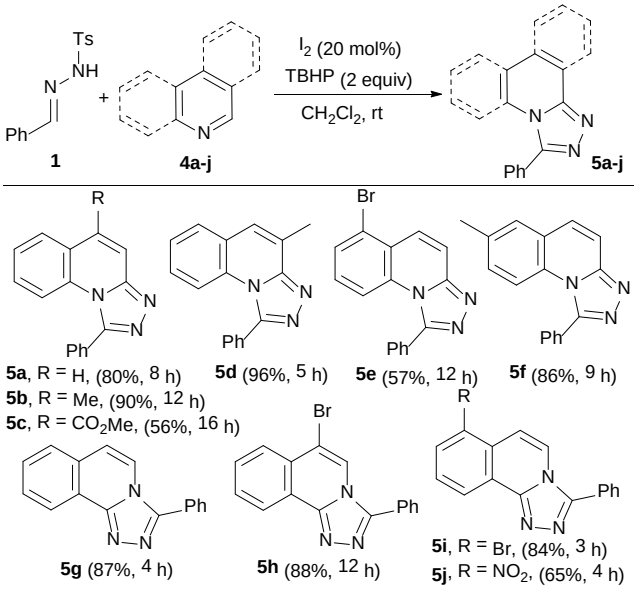
3a, R = H, 85%, 6 h
3b, R = Et, 87%, 3.5 h
3c, R = CHO, 89%, 16 h
3d, R = Ac, 92%, 11 h
3e, R = CF_3, 46%, 24 h
3f, R = CN, 41%, 16 h
3g, R = Me, 85%, 6 h
82%,[b] 6 h
3h, R = F, 65%, 16 h
3i, R = Cl, 68%, 16 h
3j, R = Br, 71%, 16 h
3k, R = CO_2Me, 68%, 16 h
3l, R = OAc, 73%, 12 h

3m, R = Me, 0%, 16 h
3n, R = F, 0%, 16 h
3o, R = H, 73%, 21 h
3p, R = Me, 69%, 24 h
3q (32%, 24 h)
3r (<10%, 16 h)

[a] Reaction conditions: **1** (0.5 mmol), **2a–r** (1.0 mmol), I_2 (20 mol%), TBHP (1.0 mmol) in CH_2Cl_2 (3.0 mL), rt (24–25 °C), time (3.5–24 h). [b] This reaction was performed on 1.0 g scale. In Parenthesis: isolated yields and reaction time.

To further explore the synthetic potential of this methodology, several quinoline and isoquinoline based substrates (Table 2, **4a–j**) were investigated under the optimized reaction condition. Unsubstituted quinoline (**4a**) and isoquinoline (**4g**) were converted to their corresponding products **5a** and **5g** respectively in high yields (80% and 87%). Both the two classes of heterocycles as reactants bearing EWG ($-CO_2$Me and $-NO_2$) afforded moderate yields of **5c** and **5j** while EDG (Me) on quinoline substrates (**4b**, **4d** and **4f**) led to higher product yields (86–96%). Notably, a halogen substitution (-Br) on the isoquinoline ring gave desired products in good yields **5h** and **5i**, however a moderate yield with quinoline (**5e**) possibly because of a favourable electronic influence in isoquinoline over quinoline.

Table 2 The substrate scope of quinoline and isoquinoline substrates[a]



1 **4a-j** **5a-j**

5a, R = H, (80%, 8 h)
5b, R = Me, (90%, 12 h)
5c, R = CO_2Me, (56%, 16 h)
5d (96%, 5 h)
5e (57%, 12 h)
5f (86%, 9 h)
5g (87%, 4 h)
5h (88%, 12 h)
5i, R = Br, (84%, 3 h)
5j, R = NO_2, (65%, 4 h)

[a] Reaction conditions: **1** (0.5 mmol), **4a–j** (1.0 mmol), I_2 (20 mol%), TBHP (1.0 mmol) in CH_2Cl_2 (3.0 mL), rt (24–25 °C), time (3–16 h). In Parenthesis: isolated yields and reaction time.

Next, we tested the compatibility and generality of the 1,3-DC catalyzed by I_2–TBHP system in a reaction using 3-methylpyridine (**2g**) and a variety of *N*-tosylhydrazones derived from diversely substituted aldehydes (Table 3, **1a–u**). The results of our studies were summarized in Table 3. Aromatic and hetero-aromatic aldehyde derived *N*-tosylhydrazones (**1a–o** and **1u**) gave excellent yields of the desired fused heterocycles (**6a–o** and **6u**) with complete regioselectivity as confirmed by single crystal X-ray diffraction analysis of **6k**.[15] *N*-tosylhydrazones (**1**) where **R** was an aryl ring bearing EWG (**1e**, **1g** and **1h**) or a hetroaryl ring (**1k–l**) afforded the desired products within a shorter reaction time (2 h) compared to electron rich aryl rings (**1c**, **1f** and **1i**). Also other heterocycles like *N*-methyl pyrazole (**1m**), furan (**1n**) and thiophene (**1o**) at **R**

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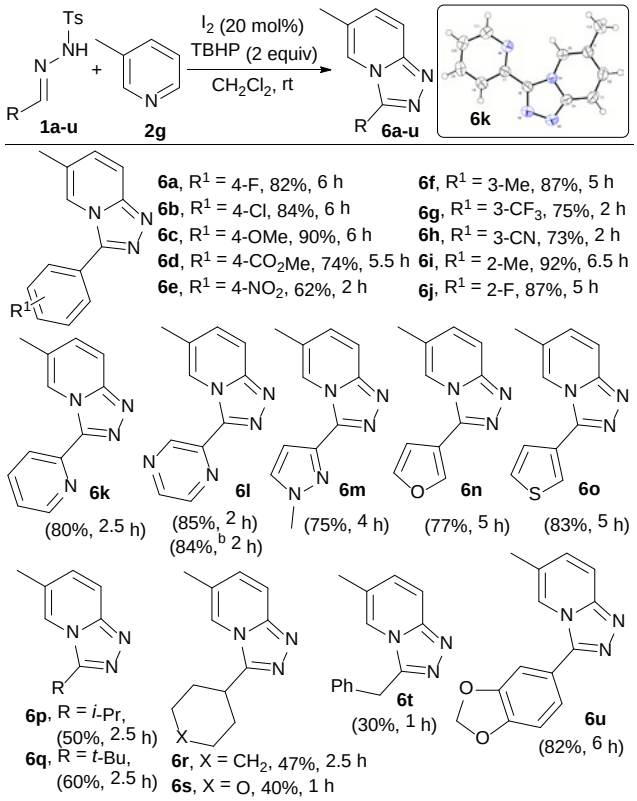
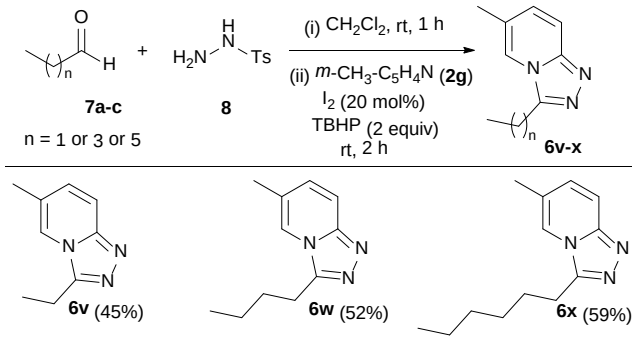
were very well tolerated to give the desired products (**6m–o**) in excellent yields 75–83%. It was noteworthy to mention that the *N*-tosylhydrazones derived from aliphatic aldehydes (**1p–s**) also offered the target fused heterocycles in moderate to good yields (**6p–s**).

Table 3 The substrate scope of *N*-tosyl aldohydrazones[a]



[a] Reaction conditions: **1a–u** (0.5 mmol), **2g** (1.0 mmol), I_2 (20 mol%), TBHP (1.0 mmol) in CH_2Cl_2 (3.0 mL), rt (24–25 °C), time (1–6.5 h). [b] This reaction was performed on 1.0 g scale. In Parenthesis: isolated yields and reaction time.

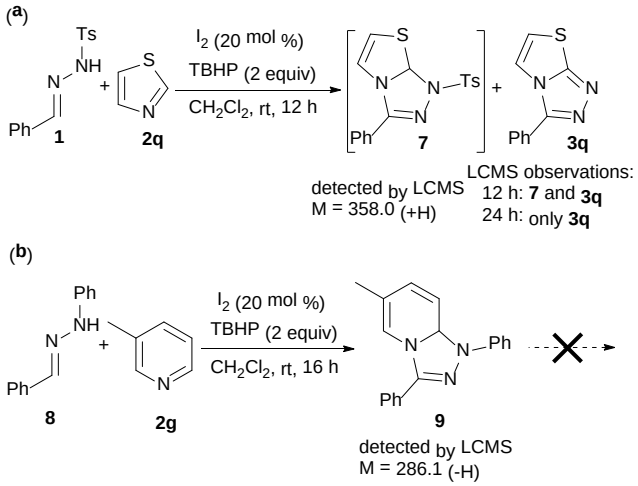
Table 4 One-pot reaction of linear chain aldehydes to triazolopyridines[a]



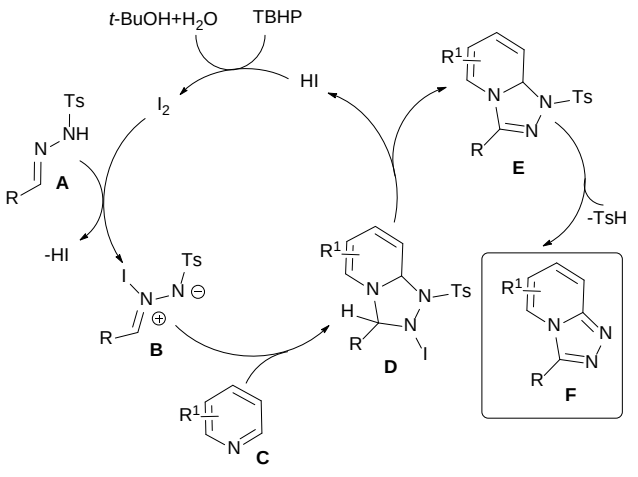
[a] Reaction conditions: **7a–c** (0.5 mmol), **8** (0.5 mmol), in CH_2Cl_2 (3.0 mL), rt, 1 h, **2g** (1.0 mmol), I_2 (20 mol%), TBHP (1.0 mmol), rt (24–25 °C), 2 h. In Parenthesis: isolated yields.

While attempting to introduce various linear alkyl groups at **R** of **1** (Table 3), the isolation of the corresponding *N*-tosylhydrazones was not successful. In order to overcome this limitation, we slightly modified the protocol where isolation of the *N*-tosylhydrazones was avoided. We initially examined the method by heptanal (Table 4, **7c**, 1 equiv) with 4-methylbenzenesulfonohydrazide (**8**, 1 equiv) in DCM (3.0 mL) stirred at room temperature for 1 h followed by addition of 3-methylpyridine (**2g**, 2 equiv), TBHP (2 equiv) and I_2 (20 mol%) stirred for another 2 h. Surprisingly, the desired compound was isolated in 59% yield (Table 4, **6x**). This protocol was further extended to propanal (**7a**) and pentanal (**7b**) to give the corresponding fused triazoles **6v** and **6w**. The results were summarized in Table 4.

Controlled reactions were performed to gain mechanistic insights into the catalytic pathway. As illustrated in Scheme 2, the intermediate **7** could be trapped in LCMS arbitrarily at 12 h time point which finally degraded into the desired product **3q**. However, the reaction with the bisarylhydrazone **8** could produce only **9,** thereby proving the necessity of the formation of intermediate **E** (Scheme 3) and hence supports the proposed catalytic cycle.



Scheme 2 Control experiments.



Scheme 3 Proposed catalytic cycle.

Based on our results, a plausible mechanism for the I_2–TBHP-catalyzed regiocontrolled cycloaddition was proposed as shown in Scheme 3. Iodine acts as a strong Lewis acid to coordinate with the nitrogen atom of the *N*-tosyl aldohydrazone **A** leading to the formation of azomethine imine dipolar complex **B** by elimination of HI. Then the unidirectional intermolecular formal [3+2]-cycloaddition between the dipolar complex **B** and dipolarophile **C** ended up with fused cycloadduct **D** followed by reductive elimination of HI to generate the fused triazoline intermediate **E**. The eliminated HI was oxidized to I_2 in the presence of TBHP and the catalytic cycle was regenerated.[16] Finally loss of TsH from **E** afforded the fused triazole product **F**.

In summary, we have developed a highly efficient one-pot methodology to synthesize structurally diverse 4,3-fused 1,2,4-triazole derivatives using the catalytic system comprising of I_2–TBHP. The reactions proceeded under mild and metal-free conditions using readily available starting substrates and gave high yields, regioselectivity and wide functional group tolerance which clearly demonstrates the unparalleled and unique reactivity of the I_2–TBHP system.

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14 For the details on the reaction condition optimization, see the ESI†.

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Table of contents

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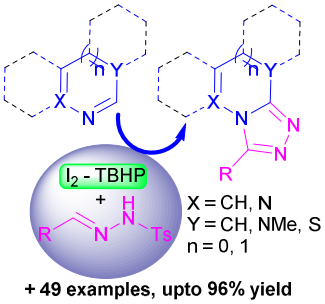

+ Metal free
+ One-pot reaction
+ Broad substrate scope
+ Green oxidant
+ High regioselectivity
+ Ambient conditions
+ Scalable