Generation of azomethine imine and metal-free formal 1,3-dipolar cycloaddition of imine with PhIO: reaction, scope, and synthesis†

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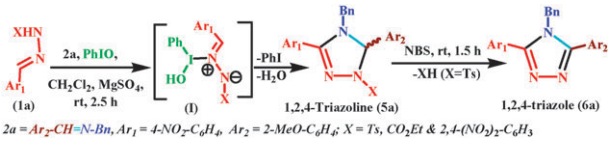
Generation of azomethine imine and its scope in regioselective 1,3-dipolar cycloaddition (DC) of imine with PhIO toward highly substituted Δ^2-1,2,4-triazoline, 1,2,4-triazole, and their fused, chiral, and sugar-based analogues are demonstrated.

Huisgen's 1,3-DC reaction has found versatile applications in organic synthesis. The powerful synthetic tool is capable of constructing bonds in a regio- and stereocontrolled way to furnish designed ubiquitous carbocyclic and heterocyclic functional molecules.[1] Cycloaddition reactions involving nitrogenous parent 1,3-dipoles like nitrile oxide, nitrone, and azomethine ylide are often investigated. Relatively less effort has been devoted for the generation and application of the azomethine imine ylides, although there is wide scope for efficient access to many valuable heterocycles. Olefins are often used for 1,3-DC reactions, where as utilization of a hetero-dipolarophile like the imine has received less attention. Metal-catalysts are usually employed for the cycloaddition of imines.[2]

Azomethine imines are generated by Huisgen's route[3a] involving condensation of aldehydes with designed 1,2-disubstituted hydrazines having certain restrictions,[3c] and subsequently cycloaddition under heating and metal Lewis acid[3d] catalyzed conditions furnish pyrazolidines and other heterocycles. Until now, there are only a few scattered methods for azomethine imine, for example, 1,4-silatropic shift of α-silylnitrosoamines under heating conditions.[3b] However, a more important and useful transformation of simple starting materials like aldohydrazones to the desired azomethine imine ylides, and their oxidative intermolecular [3 + 2]-cycloaddition with imines under mild and metal-free reaction conditions toward regioselective synthesis of Δ^2-1,2,4-triazoline, triazole and their chiral, sugar-based, and fused analogues, to the best of our knowledge, have never been realized.

The initial exploration for generation of the azomethine imine dipolar complex (**I**, Scheme 1) focused on the application of efficient metal Lewis acid catalysts[4] (entries 1–5, Table 1) on aldohydrazone (**1a**) but were in vain. Gratifyingly, attempting with the organic oxidant iodosobenzene (PhIO), utilized for our previous studies to generate 1,3-dipoles,[1c,5a] generated the dipolar complex (**I**, Scheme 1), and also rapidly (2.5 h) drove the formal [3 + 2]-DC reaction with the imine (**2a**) in an absolute regioselective way, leading to an important family of heterocycles, Δ^2-1,2,4-triazoline (**5a**, entries 6–8).[6] We have found that the choice of substituent ***Ts*** (**X**, entries 8-10) has a significant impact on the progress of the reaction. In the ongoing program to search for new low molecular mass scaffolds for self-aggregated organic architectures,[5,7] the one pot transformation of the synthon **5a** into the 3,4,5-trisubstituted-1,2,4-triazole (**6a**) was also achieved rapidly in excellent yield (95%) by the treatment of NBS (entries 11–13). However, treatment of HOBt[8] or base even under heating conditions could not undergo aromatisation with the loss of ***Ts***.



Scheme 1 Generation of azomethine imine and its applications.

The metal-free benign synthetic protocol developed under the neutral and milder reaction conditions is also an alternative approach to the nitrile imine cycloaddition reaction which is often performed utilizing unstable chloro- and bromoaldo-hydrazone precursors at higher temperature in the presence of base.[6] As part of developing a general strategy towards novel *N*-heterocycles by avoiding the isolation of unstable imine precursors (**2**), corresponding functionalized aldehydes (**3**) and primary aliphatic or aromatic amines (**4**) were taken together and stirred at ambient temperature for 6.5 h to prepare the imines (**2**) *in situ* (Scheme 2). Adoption of the multicomponent one pot strategy[9] provides great advantages over the linear multistep syntheses owing to the minimization of time, waste and manpower, and also reduction of impact on the environment and hazards. The proposed mechanistic explanation for the complete regiocontrolled cycloaddition is that PhIO herein acts as a strong Lewis acid to coordinate with the nitrogen atom of the *N*-tosyl aldohydrazone (**1**) leading to the formation of azomethine imine ylide (**I**, Scheme 2), where ***Ts*** stabilizes the negative charge. It follows the unidirectional formal [3 + 2]-cycloaddition pathways with the imine (**2**) involving the lone pair to afford the five-member heterocycles (**II**). Relative to the metal catalyzed 1,3-DC reaction it has the advantage of rapid construction of the double bond to access the Δ^2-1,2,4-triazolines (**5**) involving reductive elimination of the hypervalentiodane moiety from the putative cycloadduct (**II**). However, generation of a nitrile imine[1a,6] as a key intermediate from **1** by PhIO and the subsequent 1,3-DC with **2** toward **5** cannot be avoided. Removal of the ***Ts*** with formation of the double bond (N_2═C_3) by NBS leads to the desired heterocycles (**6**).

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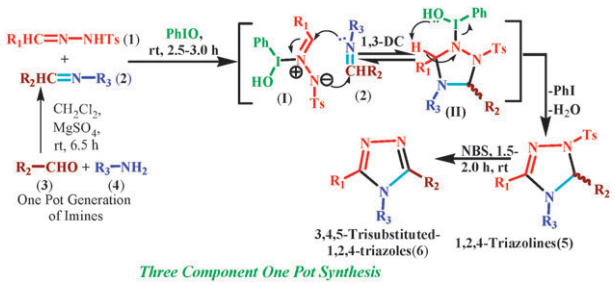
Table 1 Development and optimization of the reaction[a]

Entry	Reagents	1a/5a, X	Reaction conditions	Conversion	5a/6a,Yield(%)
1	$Ag(OTf)^b$	**1a**, Ts	CH_2Cl_2, $MgSO_4$, rt, 22 h	No reaction	**5a**, —
2	$Cu(OTf)_2{}^b$	**1a**, Ts	CH_2Cl_2, $MgSO_4$, rt, 25 h	No reaction	**5a**, —
3	$Yb(OTf)_3{}^b$	**1a**, Ts	CH_2Cl_2, $MgSO_4$, rt, 24 h	No reaction	**5a**, —
4	$Sc(OTf)_3{}^b$	**1a**, Ts	CH_2Cl_2, $MgSO_4$, rt, 28 h	No reaction	**5a**, —
5	$Ni(OAc)_2{}^b$	**1a**, Ts	CH_2Cl_2, $MgSO_4$, rt, 24 h	No reaction	**5a**, —
6	PhIO[c]	**1a**, Ts	THF, $MgSO_4$, rt, 10 h	80%	**5a**, 62[f]
7	PhIO[c]	**1a**, Ts	Me_2CO, $MgSO_4$, rt, 10 h	85%	**5a**, 65[f]
8	PhIO[c]	**1a**, Ts	CH_2Cl_2, $MgSO_4$, rt, 2.5 h	100%	**5a**, 81[f]
9	PhIO[c]	**1a**, CO_2Et	CH_2Cl_2, $MgSO_4$, rt, 3 h	100%	Dimerization
10	PhIO[c]	**1a**, 2,4-$C_6H_3(NO_2)_2$	CH_2Cl_2, $MgSO_4$, rt, 24 h	No reaction	**5a**, —
11	HOBt[d]	**5a**, Ts	MeOH, rt, 24 h	15%	**6a**[e], —
12	NBS[d]	**5a**, Ts	CH_2Cl_2, $MgSO_4$, rt, 2 h	100%	**6a**, 95
13	[g]$BuOK	**5a**, Ts	$ClCH_2CH_2Cl$, 50 °C, 8 h	60%	**6a**, 48

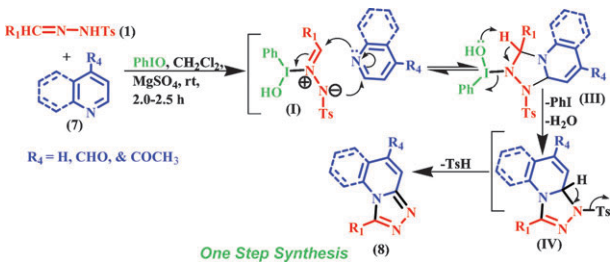
[a] Isolated yield of the compounds **5a** and **6a**. [b] Catalytic load (15 mol%). [c] Two mole. [d] Stoichiometric amount. [e] Not isolated. [f] Along with **6a** (9%). [g] Three mole.



Scheme 2 Possible pathway of the one pot synthesis.

The isolated yield was uniformly high (81–89%) for each individual case (entries 1–12, Table 2). Electron-rich and electron-deficient functional groups present in aromatic substituents were tolerated by the robust synthetic approach. Unfortunately, use of activated amine (**4d**) and 2-hydroxyphenylhydrazone (**1h**) towards formation of desired cycloadducts (**5**) were unsuccessful due to the strong chelation of PhIO with the corresponding carbanion and the phenolic-*OH* (entries 13,14). Substituted-1,2,4-triazoles (**6**) have found diverse applications as antifungal, antiviral and anticancer drugs,[10] materials,[11b] metal–ligand architectures[11c] and synthons.[11a] So far, only a limited number of synthetic approaches are reported for 3,4,5-trisubstituted-1,2,4-triazoles involving multistep reactions.[12]

The azomethine imine dipolar complex (**I**) can also be trapped even with the C=N bond of aromatic *N*-heterocycles like pyridines (**7a,b**) and quinoline (**7c**) *via* an absolute regioselective Huisgen [3 + 2] cycloaddition. To the best of our knowledge, this novel intermolecular approach towards rapid (2.0–2.5 h) access to the fused 1,2,4-triazoles (**8**, Scheme 3) is unknown in the literature. The extremely fast reaction rate can be explained by the involvement of a cascade chemical process of the highly reactive species **I** with the imine bond possessing strong electron density towards generation of the fused cycloadduct **III** and followed by reductive elimination of



Scheme 3 Intermolecular 1,3-DC with aromatic-*N*-heterocycles.

Table 2 Experimental data for synthesis of 1,2,4-triazoles (**6**)[a]

		Imine (**2**)			
Entry	Aldohydrazone (**1**, R_1)	Aldehyde (**3**, R_2)	Amine (**4**, R_3)	Reaction time/h	**6**,Yield (%)
1	*p*-NO_2–C_6H_4(**1a**)	*o*-MeO–C_6H_4(**3a**)	$CH_2C_6H_5$(**4a**)	5.0(3.0 + 2.0)	**6a**, 84
2	*β*-naphthyl(**1b**)	*p*-MeO–C_6H_4(**3b**)	$CH_2C_6H_5$(**4a**)	5.0(3.0 + 2.0)	**6b**, 88
3	*p*-Cl–C_6H_4(**1c**)	*p*-MeO–C_6H_4(**3b**)	$CH_2C_6H_5$(**4a**)	4.0(2.5 + 1.5)	**6c**, 82
4	*p*-Br–C_6H_4 (**1d**)	*p*-MeO–C_6H_4(**3b**)	$CH_2C_6H_5$(**4a**)	4.0(2.5 + 1.5)	**6d**, 81
5	*β*-naphthyl(**1b**)	*o*-BnO–C_6H_4(**3c**)	*p*-Me–C_6H_4(**4b**)	5.0(3.0 + 2.0)	**6e**, 80
6	*m*-NO_2–C_6H_4(**1e**)	*m*-NO_2–C_6H_4(**3d**)	*p*-Me–C_6H_4(**4b**)	4.5(3.0 + 1.5)	**6f**, 85
7	*p*-MeO–C_6H_4(**1f**)	*o*-NO_2–C_6H_4(**3e**)	*p*-Me–C_6H_4(**4b**)	5.0(3.0 + 2.0)	**6g**, 81
8	*p*-Cl–C_6H_4(**1c**)	*p*-Cl–C_6H_4(**3f**)	cyclohexyl(**4c**)	4.5(3.0 + 1.5)	**6h**, 88
9	*p*-Cl–C_6H_4(**1c**)	*p*-Cl–C_6H_4(**3f**)	$CH_2C_6H_5$(**4a**)	4.5(2.5 + 2.0)	**6i**,[b] 82
10	C_6H_5(**1g**)	C_6H_5(**3g**)	$CH_2C_6H_5$(**4a**)	4.5(3.0 + 1.5)	**6j**, 89
11	*β*-naphthyl(**1b**)	*m*-NO_2–C_6H_4(**3d**)	$CH_2C_6H_5$(**4a**)	4.5(2.5 + 2.0)	**6k**, 82
12	*m*-NO_2–C_6H_4(**1e**)	*m*-NO_2–C_6H_4(**3d**)	$CH_2C_6H_5$(**4a**)	5.0(3.0 + 2.0)	**6l**, 88
13	C_6H_5(**1g**)	*m*-NO_2–C_6H_4(**3d**)	$CHCO_2EtBn$(**4d**)	5.0(5.0 + -)	**6m**[c], —
14	*o*-OH–C_6H_4(**1h**)	*p*-MeO–C_6H_4(**3b**)	$CH_2C_6H_5$(**4a**)	5.0(5.0 + -)	**6n**[d], —

[a] Isolated yield. [b] Structure determined by XRD. [c] Decomposed. [d] No desired product.

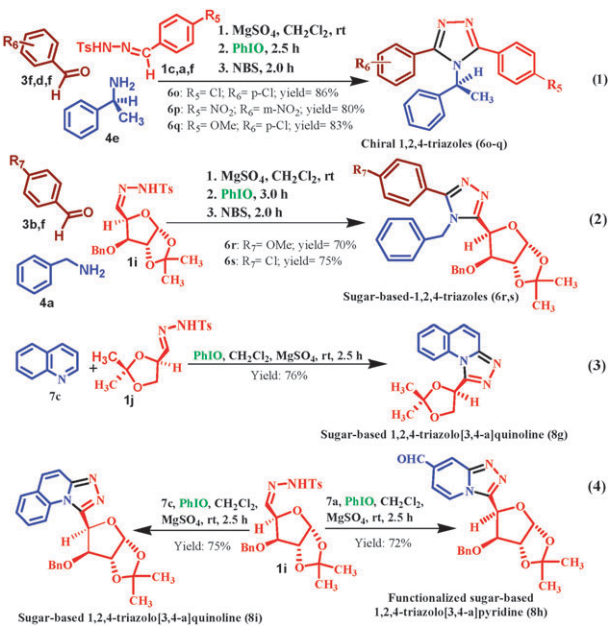
Table 3 Experimental data for synthesis of fused-1,2,4-triazole (**8**)

Entry	Aldohydrazone (**1**)	*N*-Heterocycles (**7**)	t/h	**8**, Yield (%)
1	*p*-MeO–C_6H_4(**1f**)	*p*-CHO-C_5H_4N(**7a**)	2.5	**8a**, 81
2	*p*-MeO–C_6H_4(**1f**)	*p*-$COCH_3$-C_5H_4N(**7b**)	2.5	**8b**, 79
3	*p*-Cl–C_6H_4(**1b**)	*p*-CHO-C_5H_4N(**7a**)	2.0	**8c**, 78
4	*β*-naphthyl(**1a**)	quinoline(**7c**)	2.0	**8d**, 80
5	*p*-Br–C_6H_4 (**1d**)	*p*-CHO-C_5H_4N(**7a**)	2.5	**8e**, 78
6	*m*-NO_2–C_6H_4(**1e**)	*p*-CHO-C_5H_4N(**7a**)	2.5	**8f**, 74

PhI to the fused triazoline intermediate **IV**. To regain the aromaticity, the ***Ts*** and the fused ring ***−H*** have been triggered off automatically affording the fused triazole in excellent yield (74–81%, Table 3). Thus, NBS is not required. Aldehyde, ketone and other functional groups are tolerated by the metal-free benign approach which can be utilized for further modifications. 1,2,4-Triazolo[3,4-a]pyridines and their quinoline analogues have been the focus of growing attention in the recent past for their known and potential biological activities.[13]

In contrast to the literature methods, it has no restriction regarding placement of the substitution pattern around the triazole motif (**6**) by utilizing designed precursors. We have considerably expanded the scope towards synthesis of the chiral triazoles[14] (**6o–q**, 1, Scheme 4) from the commercially available chiral aliphatic amine. Chiral 1,2,4-triazoles are well-known as drugs and fungicides.[10] Azomethine imine bearing the chiral sugar moieties can also be tolerated in this approach and efficiently utilized (2–4) for the synthesis of sugar-based 1,2,4-triazoles (**6r, s**) and their functionalized fused analogues (**8g–i**). The unnatural nucleoside analogues synthesized for the first time are potential candidates for new drug design and other applications.[15]

The structure is determined by means of X-ray diffraction (**6i**, Fig. 1) analyses.[16] It reveals the outward orientation[7,17] of all the three aromatic substituents located side-by-side and also strong intermolecular hydrogen bonding between the *p*-Cl and *o*-H atoms (2.87 Å) which have significant roles for creating the gluing non-covalent interactions among the



Scheme 4 Evaluation of precursor scope.

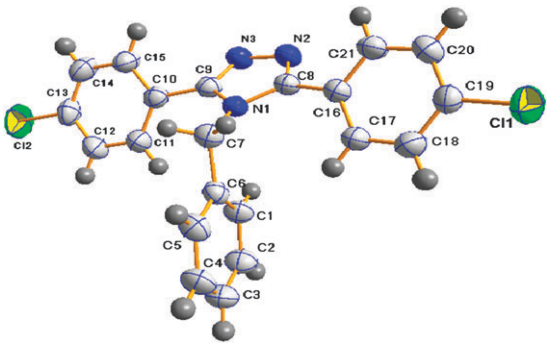


Fig. 1 Single crystal X-ray diffraction structure of compound **6i**.

neighboring molecules leading to the generation of self-aggregated low dimensional materials (ESI†).[5,7]

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16 CCD deposition code of compound **6i**: 741300.
17 Observed dihedral angles: N_1–C_8–C_{16}–C_{21} = −142.2°; N_1–C_9–C_{10}–C_{15} = +138.2°; C_8–N_1–C_6–C_5 = +97.9°.