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Transition Metal, Azide, and Oxidant-Free Homo- and Heterocoupling of Ambiphilic Tosylhydrazones to the Regioselective Triazoles and Pyrazoles

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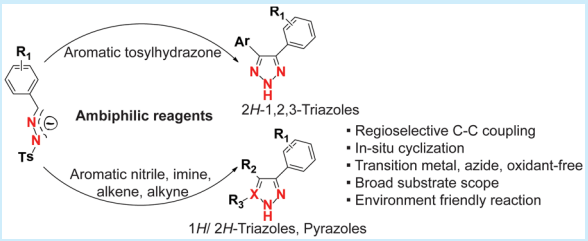
Supporting Information

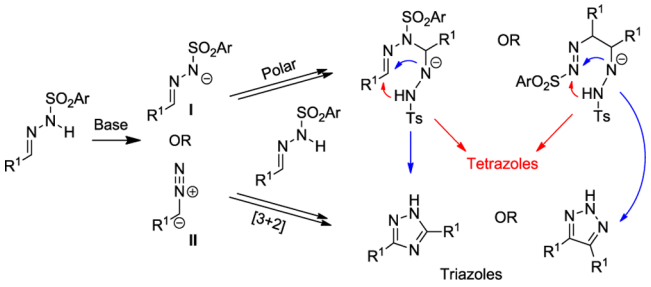
ABSTRACT: With *N*-tosylhydrazone as an ambiphilic reagent, an unprecedented cyclization reaction of two identical or different tosylhydrazones has been developed to access various 4,5-disubstituted-2*H*-triazoles under transition metal, azide, and oxidant-free conditions. A mechanistic rationalization study led to the identification of several electronically diverse unsaturated systems for regioselective synthesis of 1- and 2-substituted 1,2,3-triazoles and pyrazoles.



Tosylhydrazone was introduced to organic synthesis by Bamford and Stevens nearly 65 years ago[1] and is continuing to find new applications, predominantly via transition metal catalyzed transformations.[2] A transition metal-free diazotization for reductive coupling has emerged as well,[3] but its use as a regioselective nucleophile is underutilized,[4] with no reports on ionic dipole reactivity and regioselectivity. As part of our heterocyclic drug discovery program for cancer immunotherapy, we are focused on finding simple synthetic procedures for a quick and contaminant-free compound library. For example, regioisomeric 4,5-disubstituted 1,2,3-triazoles and pyrazoles are of interest, as they have been extensively used in bioactive molecules, pharmaceutical drugs, and synthetic intermediates.[5] However, a majority of the reported literature describes the synthesis of targeted N1-substituted 1,2,3-triazoles through a transition metal catalyzed azide−alkyne cycloaddition reaction, which restricts their use in biological sciences. The majority of the reported transition metal-free strategies used hazardous and explosive azides for the synthesis of triazoles.[6] A desirable transition metal- and azide-free synthesis remains rare with only a few multicomponent and oxidative couplings known.[7]

In that respect, we wondered if the ambiphilic nature of tosylhydrazone anion (aza-enolate, **I**) or corresponding diazo intermediate (**II**) could take part in the reaction with parent electrophilic hydrazone (Scheme 1).[8] We hypothesized that the pericyclic [3 + 2] cyclization of diazo or aza-enolate would form either 1,2,3- or 1,2,4-triazole after tosylamine elimination, but a polar mechanism[9] can lead to both triazoles as well as six-membered tetrazoles. The regio- and chemoselectivity may depend on many factors such as the intermediacy and reactivity of ambiphilic species, as well as the nature of a hydrazone electrophile. Researchers have often used alkyl, aryl, and acyl hydrazones as electrophiles, but to the best of our knowledge, no literature reports tosylhydrazones as an electrophile or sole reagent(s) for regioselective construction of triazoles.

Scheme 1. Tosylhydrazone as Ambiphilic Reagent for Heteroaromatics



We started with mild basic reaction conditions to transform a fraction of aryl-tosylhydrazone to the corresponding aza-enolate or diazo dipole keeping the starting hydrazone as the acceptor. To our delight, Cs_2CO_3 as the base and DMF as the polar aprotic solvent led to the formation of 4,5-disubstituted-2*H*-1,2,3-triazole (**3j**) even under ambient temperature as a single regioisomer (unreacted starting hydrazone remaining; Table 1, entry 1). A higher temperature and the use of 3 equiv of base (entry 4) produced the target product with a better yield. Weaker bases such as K_2CO_3, $NaHCO_3$, DBU, and DIPEA were ineffective for this transformation (Table S1 in the Supporting Information (SI)). The use of a strong base such as NaH fared poorly. Screening of solvents was carried out as well, but DMF remained the best solvent with DMSO as the only other solvent for successful triazole formation. Additional data on condition optimizations are given in Table S1 in the SI.

With optimized conditions in hand, we investigated differently substituted aryl-tosylhydrazones for the generalization of triazole

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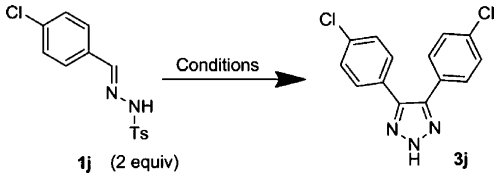
Table 1. Optimization of the Reaction Conditions for the Synthesis of 2*H*-Triazole (3j)[a]



1j (2 equiv) **3j**

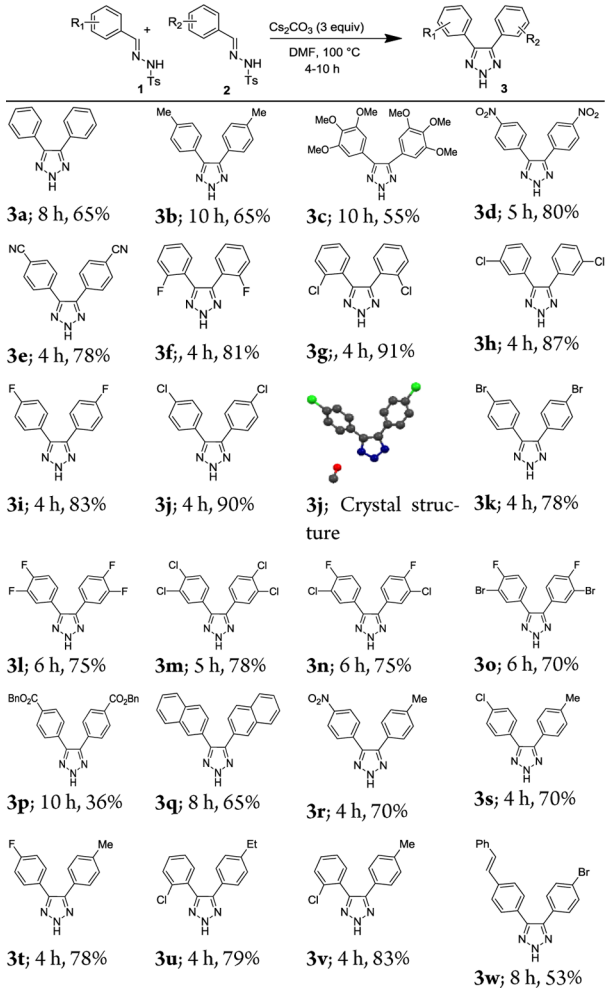
entry	base (equiv)	solvent	temp (°C)	time (h)	yield[b] (%)
1[c]	Cs_2CO_3(1)	DMF	rt	6	45
2[d]	–	DMF	100	10	–
3[c]	Cs_2CO_3 (1)	DMF	100	10	65
4[c]	Cs_2CO_3 (3)	DMF	100	4	90
5[c]	NaH (3)	DMF	100	10	45

[a]All the reactions were performed using 0.4 mmol (2 equiv) of **1j**. [b]Isolated yield of product formation. [c]5−45% Starting material **1j** was recovered. [d]100% Starting material was obtained. ND = not detected.

formation. The electronic nature of the substituted aryl group has an influence on the outcome as both the starting hydrazone electrophile and base transformed nucleophile are in conjugation with the aryl substituent (Scheme 1). For example, an electron-neutral phenyl or electron-rich aryl make the hydrazone less electrophilic and probably its deprotonation to **I** or **II** less favorable, leading to a longer reaction time and moderate yields (Scheme 2, **3a**−**3c**). On the other hand, an electron-deficient aryl group make the hydrazone more electrophilic, leading to improved yields in a shorter reaction time (**3d** and **3e**). Halogen substituted aryls are electron-deficient enough for better yields with all tested halo substituents at different positions were well-tolerated (**3f**−**3o**). The differently substituted chloro- and bromo- are of significance as they are problematic under transition metal conditions and could offer us handles for further functionalization. Fluoro substituents are becoming more important for pharmaceutically active substrates and well-tolerated with or without other substituents (**3i**, **3n**, and **3o**).[10] The use of a carbonate base tolerated the ester and cyano groups as well (**3e** and **3p**).[11] The XRD analyses also confirmed the formation of the desired 2*H*-1,2,3-triazole structure of compounds **3e** and **3j** under the experimental conditions (Figure S1 in the SI). Tosylhydrazones of aliphatic aldehydes were not compatible under the optimized reaction conditions. Synthesis of 2*H*-1,2,3-triazole, **3j**, from tosylhydrazone **1j** (2.4 g) was also studied in gram scale as a model example. As anticipated, reaction under the optimized reaction conditions yielded **3j** with a good yield (0.85 g, 75%, 4 h). The one-pot reaction of 4-chlorobenzaldehyde and tosylhydrazide under these optimized reaction conditions also produced **3j** (yield, 70%).

Such variable reactivity patterns of electronically different aryl hydrazones prompted us to attempt the heterocoupling of two hydrazones.[12] An electron-rich hydrazone will be a poor electrophile, but the dipolar reactivity will be better. The vice versa will be true for electron-poor hydrazones. The fact that we obtained a selective cross product over homocoupling of two electron-deficient hydrazones indicates the dipolar cyclization to electrophilic hydrazone as a rate-determining step. Therefore, the combination of an electron-rich dipole nucleophile and electron-poor electrophile is faster for major cross-product formation. The subtle electronic change is good enough for selective cross-coupling product formation from reactions of nitro-, chloro-, and fluoro-substituted tosylhydrazones with methyl and ethyl substituted tosylhydrazones (**3r**−**3v**). A *para*-

Scheme 2. Substrate Scope for the Synthesis of 2*H*-Triazole[a]



[a]All the reactions were performed using 0.2 mmol of **1** (1 equiv) and 0.2 mmol of **2** (1 equiv) in the presence of 0.6 mmol of Cs_2CO_3 (3 equiv) in 1.5 mL of DMF at 100 °C.

alkene substituent also changes the electronic properties adequate for the major cross-coupled product (**3w**) with the corresponding bromo-substrate (Table S2 in the SI for product distribution).

Mechanistically, the requirement of a base indicates the deprotonation of N−H of hydrazone for the generation of dipolar aza-enolate (**I**) (Scheme 3, path a). Reactions with a polar electrophile are known to proceed via this aza-enolate, but favor initial nucleophilic addition via the N-center.[4] The anionic intermediate is also known to lose Ts^- (anion) to form diazoalkanes **II** (Scheme 3, path b), which reacts with opposite regioselectivity.[13] Although hydrazone is a polar electrophile, we obtained exclusively a C-coupled product. This unusual reactivity might be an indication for the intermediacy of diazoalkanes or unusual tosylhydrazone electrophilicity. Experimental evidence such as ^{1}H NMR titration, HRMS, and GC-MS analyses also supported this proposed reaction mechanism. Formation of acylated triazole from acylhydrazone under the optimized reaction conditions also supports the dipolar mechanism since diazo or azine intermediate is unlikely with the acyl group (Figures S2 and S3 in the SI).[4a,f]

This unconventional reactivity pattern prompted us to test other electronically diverse unutilized or underutilized unsatu-

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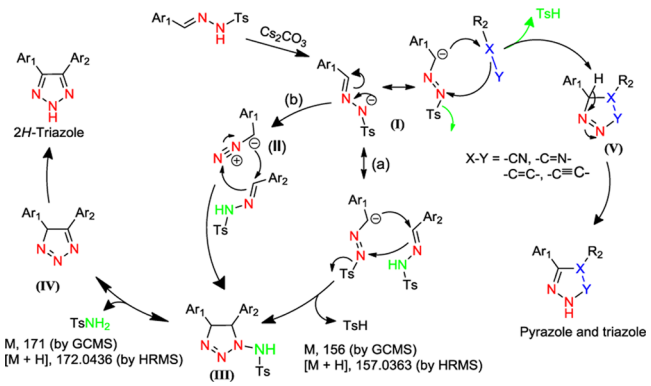
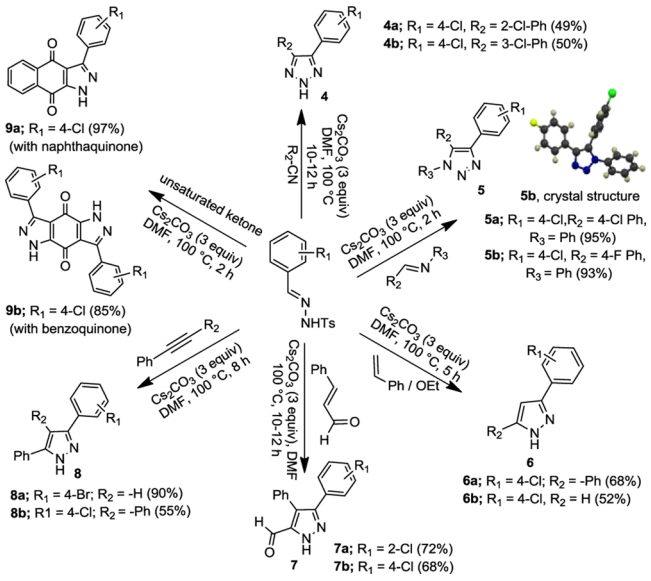
Scheme 3. Proposed Mode of Reaction under the Optimized Reaction Conditions[a]



[a]For [3 + 2] cycloaddition reaction pathway, the removal of the −Ts group could be also before the cyclization reaction (green arrow).

rated systems as coupling partners. As the electrophilic hydrazone can be considered as a traceless functional group equivalent of nitrile after tosylamine elimination to form the triazole, we first attempted to use the nitrile itself as the electrophilic coupling partner. However, nitrile turns out to be a similar and/or weaker electrophile compared to the tosylhydrazone, leading to the formation of homocoupling products along with heterocoupling with nitriles (Scheme 4, compounds **4a**, **4b**).[12]

Scheme 4. Heterocoupling of Ambiphilic Tosylhydrazones



To circumvent the reactivity and selectivity issue, we next used imine as a stronger electrophilic partner. Reaction of imine with hydrazone is very rare, and coupling with diazoalkane led to the formation of aziridine with evolution of N_2.[14] A mechanistic study indicates the formation of triazoline as an initial intermediate, which is labile under Lewis or Brønsted acid conditions to form azidirine with expulsion of N_2. We hypothesize that the triazoline intermediate will be stable under basic conditions via tautomerization (isomerization of N═N to C═N) to obtain dihydrotriazole. We started with the optimized reaction conditions for heterocoupling of tosylhydrazone and imine.

Much to our surprise, a regiospecific cross-coupled product, *N*-1 substituted triazole, was isolated (**5a**, **5b**) in good yields. We believe the presence of aerobic oxygen under basic conditions led to the oxidative aromatization of initially formed triazoline or isomerized dihydrotriazole. 2*H*-Triazole was also functionalized at the 2-position;[15] therefore, regioselective 1- and 2- substituted triazoles were obtained from either homo- and heterocoupling of tosylhydrazones or coupling of tosylhydrazone with imine.[12] XRD analysis confirmed the formation of the desired triazole structure of compound **5b** (Figure S1 in the SI).

The possibility of both aza-enolate and diazo as an intermediate prompted us to check our basic reaction protocol for coupling with alkenes and alkynes for pyrazole synthesis (compounds **6**–**9**). The tosylhydrazone coupling with a terminal alkyne and electron-rich alkenes such as *N*-vinylimidazole and vinyl acetate were tested before, but with poor to moderate yields and formation of many side products.[16] In our reaction conditions having appropriate basicity, the yields for a terminal and an internal alkyne (**8**) as well as electron-rich enol ether (**6b**) were uniformly good with significantly less side products (except a minor amount of homocoupled triazoles) mentioned in an earlier report.[12,16] Styrene reacts proficiently and auto-oxidized in air to form the pyrazole as well (**6a**). Reaction with electron-deficient alkenes such as cinnamaldehyde and quinone produced good to excellent yields of pyrazole with a negligible amount of side product (**7** and **9**).

In conclusion, tosylhydrazone was utilized as both a traceless tosyl activator for an ambiphilic dipole as well as a traceless tosylamine activator substituent for nitrile. The homo- and heterocoupling led to the synthesis of regioselective 4,5-disubstituted-2*H*-1,2,3-triazoles in good yield, and coupling–auto-oxidation with imine led to the formation of N1-substituted 1,2,3-triazoles. The aryl-tosylhydrazone was identified for its versatile coupling potential and coupled with electronically diverse alkenes and alkynes for regioselective pyrazole synthesis. This transition metal, azide, and oxidant-free reaction conditions allow a broad range of functional group tolerance, which can be a useful alternative to the existing methods for the synthesis of regioselective *N*-heterocyclic compounds such as triazoles and pyrazoles. The library synthesis and biological evaluation on cancer immunotherapy are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00313.

Experimental procedures and spectroscopic data for all compounds; HR-ESI-MS, IR data; crystallographic information for compounds **3e**, **3j**, and **5b** (PDF)

X-ray data for compounds **3e**, **3j**, and **5b** (CIF)

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Notes

The authors declare no competing financial interest.

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(15) 2-Methyl-4,5-bis(4-chlorophenyl)-2*H*-1,2,3-triazole (**10**) was synthesized from compound **3j** in good yield (83%, 8 h).
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