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Accelerating Effect of Triazolyl and Related Heteroaryl Substitutents on S_NAr Reactions: Evidence of Hydrogen Bond Stabilized Transition States

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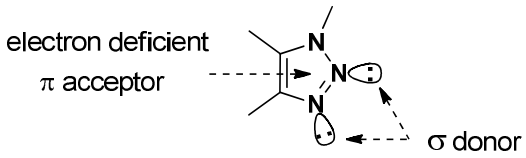
ABSTRACT: The remarkable accelerating effect of 1,2,3-triazolyl substituents on S_NAr reactions has been investigated through systematic experiments and density functional theory calculations. The lone pair electrons of an *ortho*-triazolo substituent play a key role in lowering the activation energy for nucleophilic addition via formation of a preferential hydrogen bond with the amine nucleophile at the transition state for addition. In an extension of this finding, a series of related heteroaryl groups with similar electron pair donor properties have also been found to facilitate S_NAr reactions. The experimentally determined solvent effect provides further support for this rationale, which was utilized to achieve an *ortho*-selective substitution on a difluoroarene substrate.

INTRODUCTION

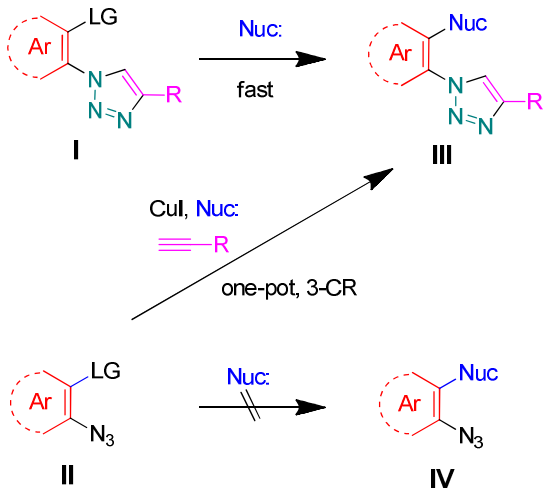
Since the discovery of the copper catalyzed azide-alkyne cycloaddition reaction (CuAAC, click chemistry), 1,2,3-triazole has become one of the most studied heterocycles in chemical, biomedical and material research in the past decade.[1-3] Apart from its efficient formation and remarkable stability, the unique electronic properties of this heterocycle are also of great interest (Figure 1). On one hand, incorporation of two extra electronegative nitrogen atoms makes this heterocycle a more electron-deficient aromatic system (π-acceptor) compared to other five-membered rings such as pyrrole. On the other hand, these two nitrogen atoms also possess lone-pair electrons orthogonal to the π-system. This σ donor property has been applied in some recent transition metal catalyzed reactions in which the triazole ring was utilized either as an important part of the catalytic ligands or as a built-in directing group on the reaction substrates.[4,5] Beyond metal complexation, however, the influence of this unique heterocycle on the chemical reactivity of its neighboring groups remains largely unexplored.

Figure 1. Dual electronic properties of 1,2,3-triazole.



In a recent medicinal chemistry program, we observed an unexpected, significant activating effect of the triazolyl substituent on the S_NAr–type reaction. As illustrated in Scheme 1, treatment of a triazolyl substituted substrate **I** with a nucleophile led to a facile conversion to **III**. In a control experiment, the corresponding azide **II** failed to afford S_NAr product **IV** under the same conditions. Based on this observation, we have developed a general "click and activate" strategy for multiple component synthesis of heterocycle libraries. In this protocol, a leaving group-conjugated azide **II,** serving as an unactivated electrophile, was compatible with the presence of both an alkyne and a nucleophile in a single pot, due to the specific reactivity profile of azide and the alkyne. Addition of a copper catalyst to this mixture not only led to the efficient union of the azide **II** and the alkyne, but also triggered the subsequent substitution reaction with the nucleophile, achieving a rapid assembly of molecular diversity.[6-8] The successful application of this protocol in diversity-oriented synthesis stimulated our interest to fully understand the origin of this intriguing activation effect of triazole.

Scheme 1. Activation effect of triazolyl group on S_NAr reactions and its application in multiple component reactions.



The S_NAr reaction is one of the most important tools in the functionalization of aromatic and heteroaromatic rings. The substituent effects of common electron-withdrawing groups, such as nitro, cyano, sulfonyl, keto, ester, or amide groups on the rate of S_NAr reaction have been well documented.[9,10] However, to the best our knowledge, the effects of heterocyclic substituents (including the triazolyl group) on this classical transformation have been largely overlooked.

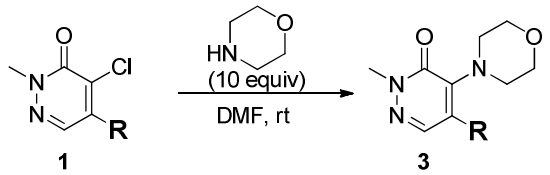
In this paper, we explain the origin of this accelerating effect through detailed control experiments and density functional theory calculations, using pyridazinone core **1** as the substrate (Figure 2).[11] It was further determined that triazole is not the only heterocycle to exhibit this effect, as was predicted theoretically and experimentally validated for other heteroaromatic substituents (R group in **1** below.). Lastly, it is demonstrated that this type of triazole group activation is general and can be applied to S_NAr reactions on broader aromatic substrates **2**.

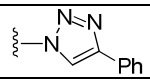
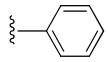
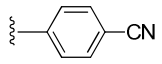
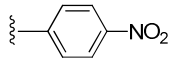
Figure 2. Two types of substrates in this study.

RESULTS AND DISCUSSION

Initially, the observed rate accelerating effect of the *ortho* triazole on the S_NAr reaction depicted in Scheme 1 was simply attributed to the mild electron-withdrawing property of the triazole moiety. To confirm this hypothesis, 4-chloro-pyridazinone analogs **1b-1e** with gradually stronger electron-withdrawing substitutents at the neighboring 5-position were prepared and compared to triazole **1a** in reactions with morpholine in DMF (Table 1). To our surprise, even the strongest electron-withdrawing *para*-nitrophenyl group (**1e**) in this series, as gauged by both substrate LUMO energy and relative electron affinity *(vide infra)* exhibited far less activating effect (undetectable under our control experiment conditions) compared to the remarkable rate accelerating effect of the triazole (**1a**).

Table 1. Initial control experiments with electron-deficient phenyl substituents.



Substrate	R	% conversion[a,b] (1h)	% conversion[a,b] (6h)	% conversion[a,b] (24h)	LUMO Energy[c] (Hartrees)	Relative electron affinity[d] (kcal/mol)
1a		60	100	ND	+0.04086	10.0
1b	N_3	0	0	0	+0.04928	2.2
1c		0	0	0	+0.05616	0[e]
1d		0	0	0	+0.03196	14.5
1e		0	0	0	+0.01863	24.8

[a] The reactions were conducted at 0.1 M substrate concentration.

[b] Conversion was calculated based on HPLC peak integration at 254 nm.

[c] From RHF/6-31G* single-point energies of B3LYP/6-31G* optimized geometries.

[d] Relative electron affinities obtained from (U)B3LYP/6-31+G** single-point energies of (U)B3LYP/6-31G* optimized neutral and radical anion geometries.

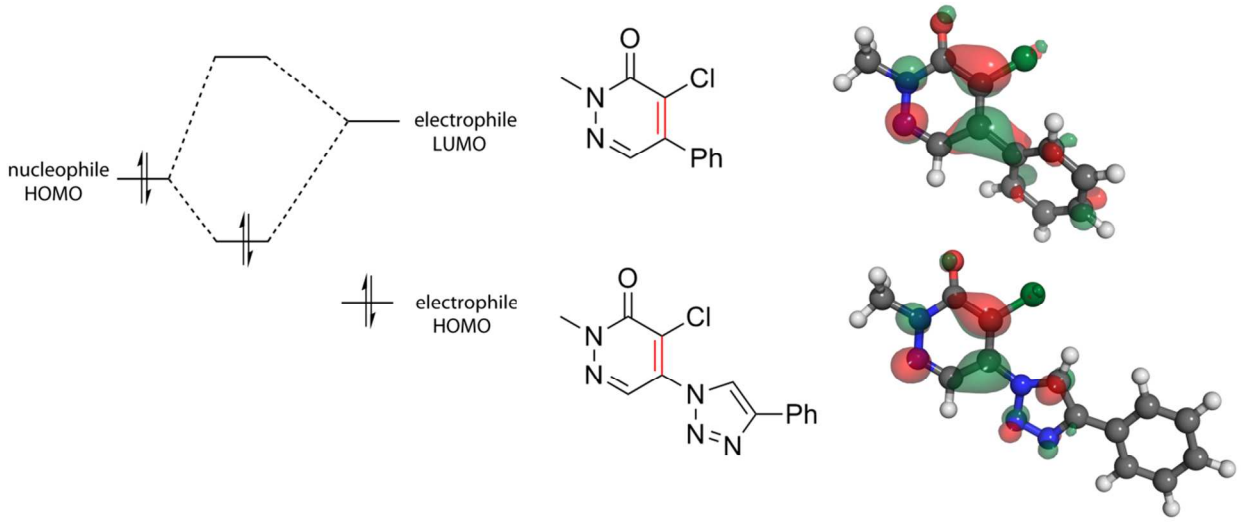
[e] Parent phenyl-substituted system **1c** used as reference value (Relative electron affinity **1c** = 0.0 kcal/mol)

This unexpected result prompted a computational investigation of the intrinsic electrophilicity of substrates **1a**-**1e**.[9,10] For reactions between a given nucleophile and a class of homologous electrophilic substrates possessing a similar steric footprint, the kinetics of addition should be governed to a significant extent by the LUMO of the substrate (Figure 3). A lower substrate LUMO energy gives rise to a lower HOMO-LUMO gap, and hence a greater degree of reactivity. The LUMO of systems **1a** and **1c** above, found to be primarily localized at the C=C π^* where the S_NAr reaction was found to take place for all substrates, are depicted in Figure 3.

As expected, the increase in predicted relative adiabatic electron affinities reported in Table 1 track identically with successively lower LUMO energy, with the overall electrophilicity of **1a** predicted to lie between phenyl- and cyanophenyl-substituted substrates **1c** and **1d**, respectively. Thus it is clear that triazole system **1a** possesses substantially greater reactivity

toward morpholine addition than would be predicted based solely on inherent substrate electrophilicity.

Figure 3. FMO interaction diagram and substrate LUMOs (RHF/6-31G*; 0.05 a.u. contour level) of systems **1a** and **1c.**

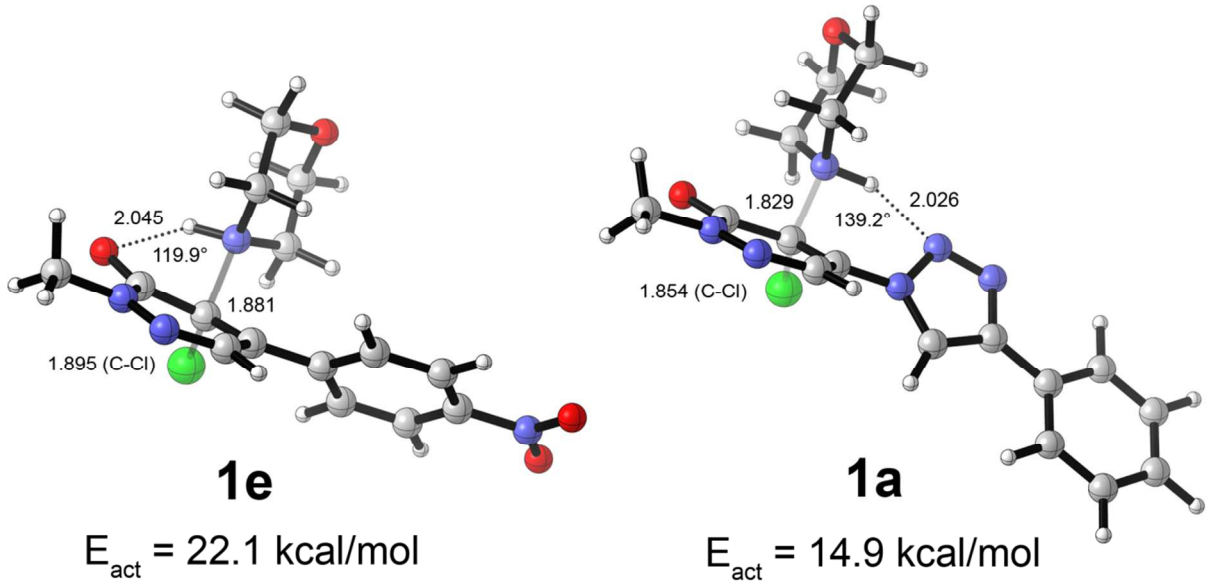


Since simple substrate-based electronic factors were not sufficient to explain the unique activation effect of triazole in this case, we shifted our attention to the other structural feature of this heterocycle, the σ donor property. We reasoned that the central nitrogen atom (2-N) of the triazole moiety might enable an internal hydrogen bonding interaction with the incoming amine nucleophile. This hypothesis is related to the concept of a "built-in-solvation" effect, first proposed by Bunnett.[12] This concept has been used to describe the favorable interactions between nucleophiles and various *ortho* accelerating groups in the transition state of the S_NAr reaction through hydrogen bonding, electrostatic attraction, or metal counter ion coordination. Nevertheless, the rare and scattered reports on this subject in the past six decades have only been rationalized by conceptual images with little theoretical support.[13,14] Moreover, only small functional groups such as nitro, keto, carboxylate, ester and amide groups have been evaluated experimentally. To the best of our knowledge, there has been no systematic investigation of aromatic heterocycles as the *ortho*- activating groups in simple S_NAr reactions in the literature. Thus, the structural and energetic features of the transition structures for morpholine addition to a variety of substrates were investigated in detail herein.

Figure 4 depicts the lowest energy B3LYP/6-31G* transition structure (TS) for the concerted, 1-step morpholine addition to 4'-nitrophenyl substituted substrate **1e**, within which a

hydrogen bonding interaction is predicted to occur between the carbonyl oxygen of the pyridazinone core and NH of the morpholine nucleophile.[15] In contrast, in the presence of the triazole substitutent (**1a**), a hydrogen bond involving the central 2-N of the triazole is instead more favorable, representing the lowest energy TS.[16] The 7.2 kcal/mol preference for the 6-membered TS involving intramolecular triazole complexation over the corresponding 5-membered TS for **1e** is in direct accord with the results of the control experiments in Table 1, and provided a working rationale for the significant accelerating effect of triazole group on the S_NAr reaction. A portion of the preferential stabilization of the TS for **1a** may also be attributed to the larger (ca. 139°) ∠N-H···N angle at the TS for **1a**, significantly closer to an ideal donor-acceptor angle (180°) than for **1e** (∠N-H···O ca. 120°) along with a more favorable orientation of the triazole N versus carbonyl O lone pair.

Figure 4. Lowest energy transition structures for morpholine addition to substrates **1e** and **1a** (B3LYP/6-31G*.) Distances denoted in Ångstroms, angles in degrees.

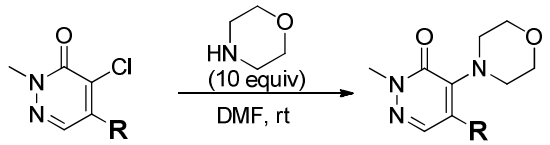


Intrigued by the structural and energetic aspects of the respective transition structures, we subsequently extended our investigation to additional heteroaromatic and other appropriately-oriented, σ-electron donating groups in the same pyridazinone scaffold (Table 2). The B3LYP/6-31G* geometries of the morpholine nucleophile, substrates, and lowest energy transition structures were further optimized utilizing the large and diffuse *aug*-cc-pVTZ basis, and found to track well (albeit with higher absolute E_{act} values) compared to the B3LYP/6-31G*

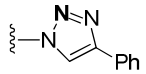
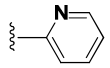
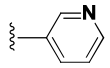
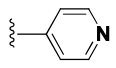
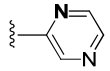
results. Comparison of the three regioisomeric pyridyl groups **1f-1h** provided the most compelling demonstration of this stabilizing effect. In compound **1f**, the 2-pyridyl group, approximately isosteric and isoelectronic with respect to the triazolyl group in **1a**, offered a similar, experimentally-determined rate acceleration in the S_NAr reaction. This is in agreement with the relatively low predicted E_{act} , involving a TS which is stabilized by a hydrogen bond involving the 2-N atom of the pyridine ring (Figure 5). Relocation of this hydrogen bond acceptor, as in the cases of 3- and 4-pyridyl analogs, removes the favorable 6-membered network in the TS, necessitating stabilization by the pyridazinone carbonyl oxygen instead and raising the predicted E_{act} by ca. 8 and 7 kcal/mol for **1g** and **1h**, respectively. As a result, both **1g** and **1h** are nearly inert towards the nucleophile under the same conditions, despite 4-pyridyl substrate **1h** possessing a greater inherent electrophilicty than 2-pyridyl-substituted analog **1f** as gauged by both LUMO energy and electron affinity (Table 2). The more π-electron deficient pyrazine derivative **1i** is slightly more reactive. Five-membered heterocycles, represented by thiazole (**1j**) and oxazole (**1k**) also exhibit a remarkable rate accelerating effect. Interestingly, while two different heteroatoms are available at the proper location for morpholine stabilization in oxazole **1k**, the nitrogen atom is clearly preferred as the hydrogen bond acceptor in the lowest energy TS (Figure 5)[17,18] The inferior hydrogen bond acceptor capacity of the heterocyclic oxygen atom was further showcased by the 2-furanyl substituent in **1l**, offering no assistance in lowering the energy of the TS. Accordingly, no rate acceleration was observed experimentally for **1l**.

In general, keto and ester groups are more electron withdrawing than most aryl and heteroaryl groups. At the same time, the *ortho*- carbonyl group were found to act as a powerful hydrogen bond acceptor to the amine hydrogen to stabilize the cyclic TS, thus significantly lowering the barrier to reaction (Figure 5) in addition to their electron-withdrawing nature in the classical sense[14b,c] As expected, both ketone **1m** and ester **1n** are highly reactive towards morpholine and the S_NAr reactions, reaching completion within 10 minutes. The extreme facility by which system **1m** undergoes reaction compared to cyanoaryl species **1d** (Tables 2 and 1 respectively), despite possessing similar inherent substrate electrophilicities, further underscores the importance of the hydrogen bonding ability of the *ortho* substituent at the TS for nucleophile addition.

Table 2. Product conversions (%) and predicted activation barriers (at the B3LYP/6-31G* and B3LYP/*aug*-cc-pVTZ levels) demonstrating activating effect of triazole and other related heterocycles.



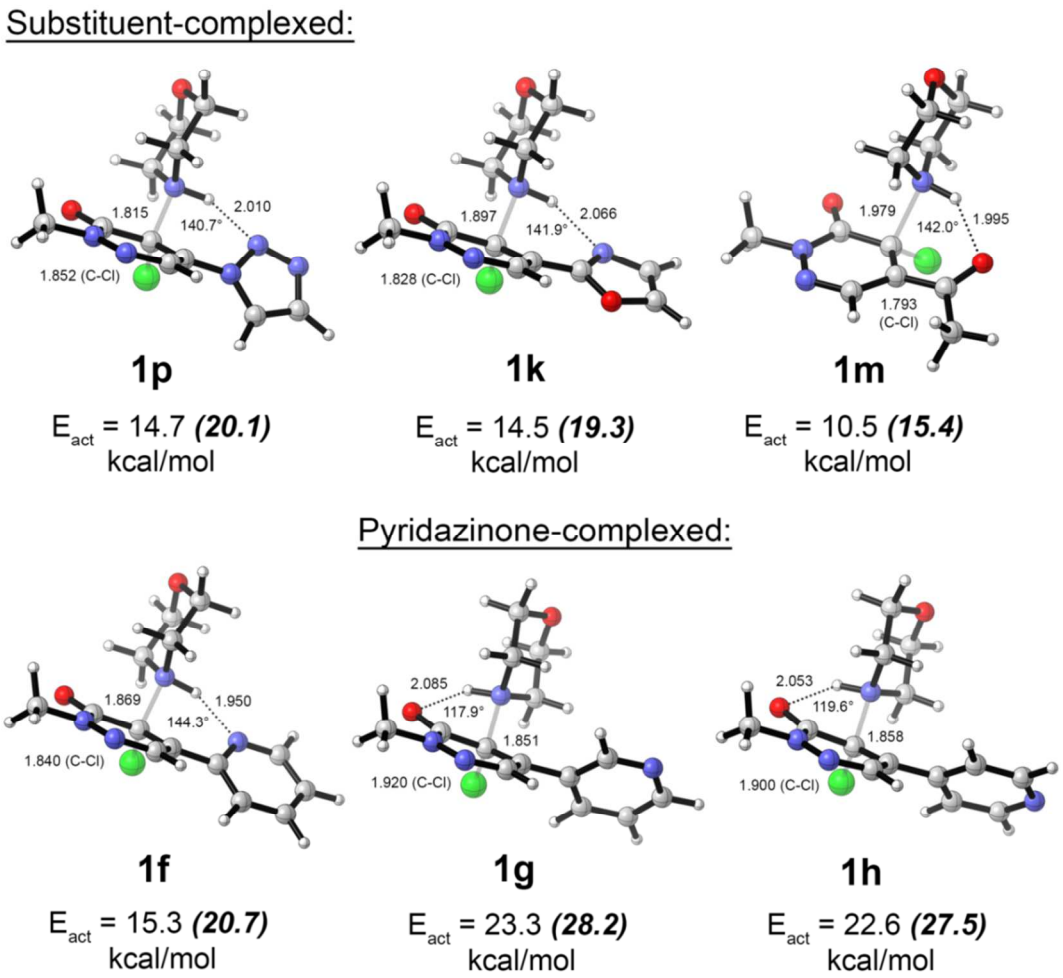
1 3

Substrate	R	% conversion[a,b] (1h)	% conversion (6h)	% conversion (24h)	LUMO energy[c] (Hartrees) / Relative electron affinity[d,e] (kcal/mol)	E_{act} (kcal/mol)[f,g]
1a		60	100	ND	+0.04086/ 10.0	14.9 / 14.7 [h] ***(20.1)*** [h]
1f		30	72	100	+0.04768/ 4.3	15.3 ***(20.7)***
1g		0	0	0	+0.04862/ 4.9	23.3 ***(28.2)***
1h		0	0	4	+0.04304/ 8.2	22.6 ***(27.5)***
1i		65	100	ND	+0.03782/ 10.4	14.8 ***(20.3)***
1j		57	92	100	+0.03379/ 12.3	12.2 ***(17.6)***
1k		100	ND	ND	+0.03425/ 6.7	14.5 ***(19.3)***
1l		0	0	0	+0.04497/ 0.7	22.7 ***(27.7)***
1m		100	ND	ND	+0.03048/ 13.6	10.5 ***(15.4)***
1n		100	ND	ND	+0.03540/ 9.6	10.6 ***(16.4)***

- [a] Reactions were conducted at 0.1 M substrate concentration
- [b] Conversion was calculated based on HPLC peak integration at 254 nm.
- [c] From RHF/6-31G* single-point energies of B3LYP/6-31G* optimized geometries.
- [d] Relative electron affinities obtained from (U)B3LYP/6-31+G** single-point energies of (U)B3LYP/6-31G* optimized neutral and radical anion geometries.
- [e] Parent phenyl-substituted system **1c** used as reference value (Relative electron affinity = 0.0 kcal/mol)
- [f] B3LYP/6-31G* + ZPE versus separated reactants.
- [g] Bold parenthesized values indicate B3LYP/*aug*-cc-pVTZ + ZPE versus separated reactants.

- [h] Data for parent unsubtituted (*des*-phenyl) triazole analog **1p** due to poor SCF convergence behavior for larger analogs.

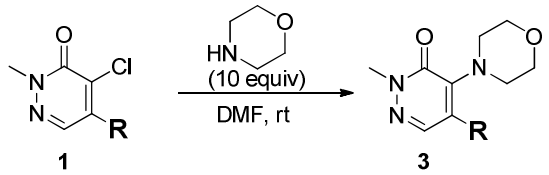
Figure 5. Structural parameters (B3LYP/aug-cc-pVTZ) and E_{act} values (B3LYP/6-31G* and B3LYP/aug-cc-pVTZ; latter in bold italic; kcal/mol) for morpholine addition to heteroaryl- and acyl-substituted substrates **1p**, **1k**, **1m** (alternate view) and **1f-1h**. Distances denoted in Ångstroms, angles in degrees.

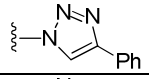
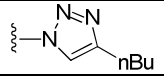
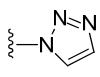
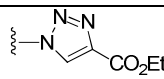
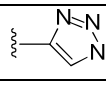


Next, the influence of different substituents on the triazole moiety was systematically studied, with results reported in Table 3 below. While *N*-linked triazoles **1o** and **1a,** possessing alkyl and phenyl groups at the 4'-position, showed little difference in reaction rates, the 4,5-unsubstituted triazole analogue **1p** was found to be slightly more reactive. An electron-withdrawing ester group at the 4-position of the triazole further activated the substrate **1q** as the

electrophile. Surprisingly, the "reversed", C-linked triazolyl group in **1r** was found to be significantly less reactive, despite the availability of the 3-N atom on the triazole ring for hydrogen bond formation with the incoming morpholine nucleophile. In addition to the inherent increase in electrophilicity between **1a** and **1r** as gauged by LUMO energy and electron affinity (*vide infra*), this significant isomeric effect can be further explained by the electrostatic potential-derived atomic charges of the regioisomeric nitrogen atoms in the triazole ring of the substrate (Figure 6). In general, the central 2-N is found via electrostatic potential calculations to be more electron rich in both N- and C-linked scenarios by ca. 0.08 – 0.1 electrons, and thus should act as a better hydrogen bond acceptor than the corresponding 3-N atom. The starkly differing electrophilicities and hydrogen bond acceptor capacity is reflected in a ca. 4 kcal/mol difference in E_{act} between the two regioisomers **1a** and **1r**.

Table 3. Product conversions (%) and predicted activation barriers (B3LYP/6-31G*) for various substituted and regioisomeric triazolyl substrates.

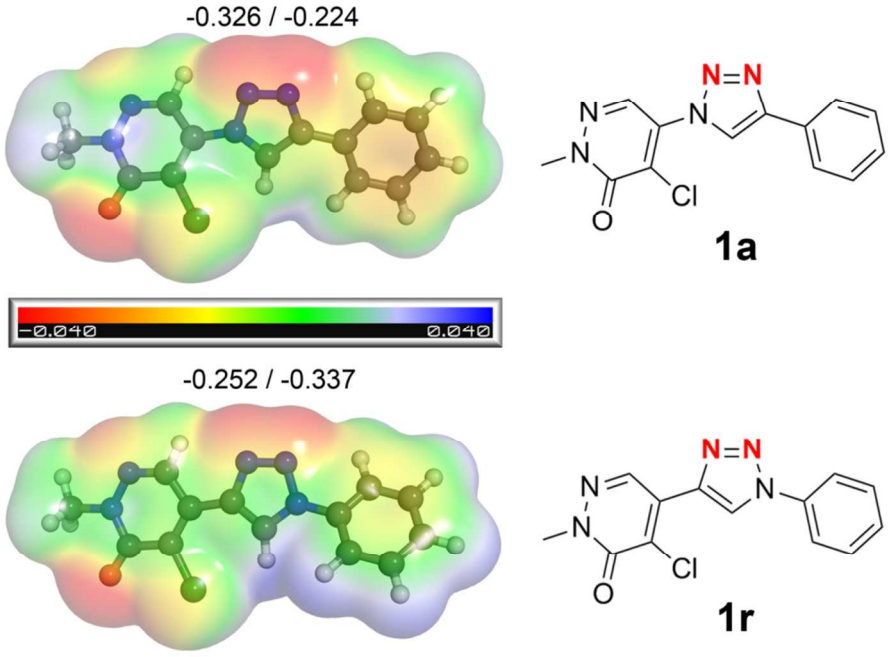


Substrate	R	% conversion[a,b] (1h)	% conversion (6h)	% conversion (24h)	LUMO energy[c] (Hartrees) / Relative electron affinity[d] (kcal/mol)	E_{act} (kcal/mol)[e]
1a		60	100	ND	+0.04086 / 10.0	14.9
1o		56	100	ND	+0.04466[f] 6.5	15.1
1p		90	100	ND	+0.04172 8.0	14.7
1q		100	ND	ND	+0.03436[g] 13.0	14.1
1r		4	10	25	+0.04996 4.2	19.2

- [a] The reactions were conducted at 0.1 M substrate concentration
- [b] The conversion was calculated based on HPLC peak integration at 254 nm.
- [c] From RHF/6-31G* single-point energies of B3LYP/6-31G* optimized geometries.

- [d] Relative electron affinities obtained from (U)B3LYP/6-31+G** single-point energies of (U)B3LYP/6-31G* optimized neutral and radical anion geometries.
- [e] B3LYP/6-31G* + ZPE versus separated reactants.
- [f] Theoretical data for methyl-substituted triazole.
- [g] Theoretical data for methyl ester-substituted triazole.

Figure 6. Molecular electrostatic potentials (a.u. ; 0.001 a.u. contour level; B3LYP/6-31G*) and resultant atomic charges (electrons) of the 2-N and 3-N of the triazole ring.

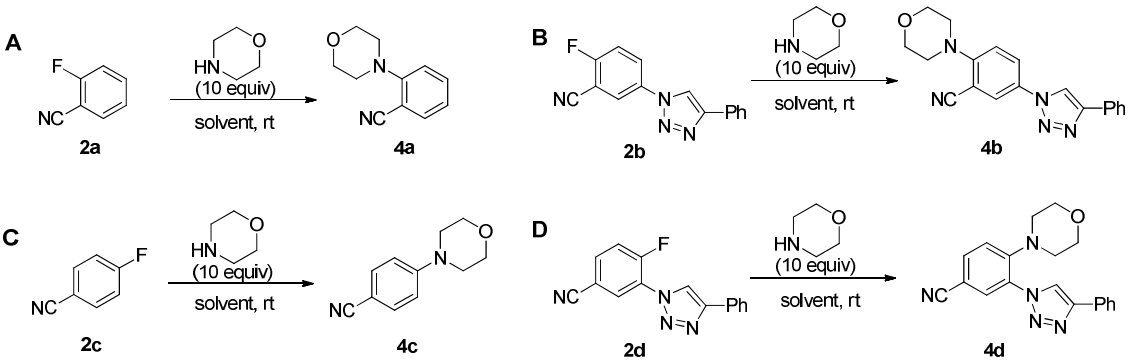


Having fully rationalized the activation effect of the *ortho*-heteroaryl groups on the pyridazinone platform, we expanded our investigation scope to the more general benzene substrates (Table 4).[19] In the control experiments, both 2-fluoro- and 4-fluorobenzonitriles (**2a** and **2c**) were found to react slowly with morpholine in DMF. In this case, the cyano group was chosen because it cannot form a cyclic transition state with the amine nucleophile due to its linear geometry. The observation that 2-fluorobenzonitrile reacted slower than the 4-fluoro analogue is possibly due to the intrinsic electronic difference and/or steric hindrance of the *ortho*- substitution pattern. Introducing a triazolyl group *para*- to fluorine in **2a** enhanced the reaction rate (**2a** and **2b**). This indicated that the remote triazolyl group exhibits a moderate electron-withdrawing effect on the benzene substrate. As expected, a triazolyl substitution

ortho- to fluorine in **2d** provided an even more significant acceleration as the combined result of both electronic and the hydrogen bonding assisted TS effects.

The importance of the hydrogen bonding assisted TS was further demonstrated in the solvent effect on this set of substrates. It is well known that solvents with high dielectric constant and high solvent hydrogen bond basicity such as DMF (ε_r = 36.71 and pK_{HB} = 2.10) generally favor S_NAr reactions by stabilizing charge separation in the transition states or intermediates.[14,20] In comparison, the same reactions in Table 4 in the less polar and less hydrogen bond basic solvent 1,4-dioxane (ε_r = 2.21 and pK_{HB} = 1.03) are much slower. As expected from our rationale, the gap of the relative reaction rates between the two isomeric substrates **2b** and **2d** becomes much more pronounced. While **2b** is completely unreactive in this solvent, **2d** still undergoes a steady S_NAr reaction due to the assistance from the neighboring triazolyl group via hydrogen bonding interaction.

Table 4. Triazole-accelerated S_NAr reactions on benzene core.

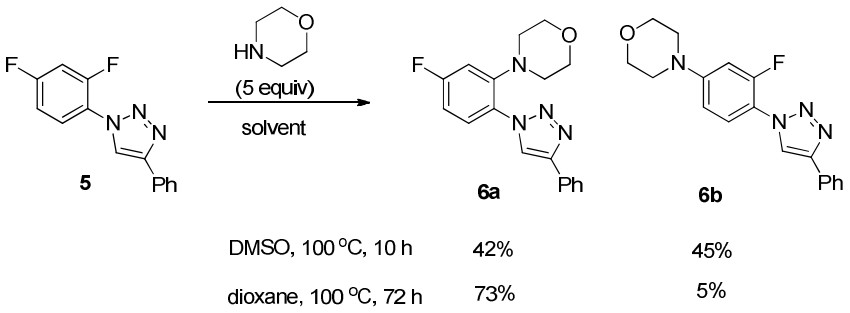


Reaction (solvent)	% conversion (1h)[a,b]	% conversion (6h)	% conversion (24h)
A (DMF)	0	3	9
B (DMF)	10	30	60
C (DMF)	2	12	32
D (DMF)	51	100	ND
A (dioxane)	0	0	0
B (dioxane)	0	0	0
C (dioxane)	0	0	0
D (dioxane)	3	29	65[c]

- [a]Reactions were conducted at 0.1 M substrate concentration.
- [b]Conversion was calculated based on HPLC peak integration at 254 nm.
- [c]91% conversion at 48 h.

The differentiation of the two activation modes by triazole (or other related heterocycles) in different solvents can be utilized to achieve high regioselectivity on aromatic substrates with more than one leaving groups such as **5** in Scheme 2. Electronically, both the *ortho*- and the *para*- (fluoro) positions of **5** are activated by the moderately electron-withdrawing triazolyl moiety (as the only activating group).[21] Therefore, S_NAr reaction with morpholine in highly polar and highly hydrogen bond basic solvent DMSO (ε_r = 46.45 and pK_{HB} = 2.58) led to a nearly 1:1 *ortho*- and *para*- isomers **6a** and **6b**. On the other hand, because only the *ortho*-position is capable of forming a hydrogen bond assisted six-membered TS with the incoming nucleophile, a high *ortho*-selectivity (~15:1 *o/p* ratio) can be obtained in dioxane, which has poor hydrogen bond forming capability and low polarity. In control experiments, no substitution product could be observed on 1,3-difluorobenzene under the same conditions in either solvents.

Scheme 2. Triazole-directed regioselective S_NAr reaction on difluoroarene **5**.



CONCLUSION

In summary, we have demonstrated that an *ortho*-1,2,3-triazole substituent can provide a significant accelerating effect on the S_NAr reaction due to its dual electron acceptor/donor properties. Compared to its moderate electron-withdrawing effect, the capability of forming a preferential hydrogen bond with the amine nucleophile can sometimes play a more important role in stabilizing the transition state and lowering the activation energy. Extension of this rationale led to the first systematic investigation and discovery of various related heteroaryl substitutions that facilitate S_NAr reaction under the similar mechanism. The different degree of activation between the N-linked triazole and the "reversed", C-linked triazole highlights the importance of the lone pair electron richness (2-N > 3-N) in determining the strength of hydrogen bond in the transition state in addition to the inherent electrophilicity. The same hypothesis is further supported by control experiments in different solvents and enables an *ortho*-

selective substitution on a difluoroarene substrate. Combined with the remarkable compatibility of azides and alkynes with various nucleophiles and electrophiles, this triazole activation effect provides unique opportunity in the design of conceptually novel multiple component reactions.[6-8] Further experimental and computational studies are underway to understand other related heteroaryl assisted reactions.

ASSOCIATED CONTENT

Supporting Information

Detailed description of experimental procedures and characterization data, ^{1}H and ^{13}C NMR spectra for compounds **1-6**, and full description of theoretical methodology, including geometric and energetic data for reactants and transition structures for systems **1a-1r**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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15. In the case of our pyridazinone / morpholine systems, the reactions were found to be concerted on the B3LYP surface. In the literature, various kinetic and computational studies have demonstrated that the preference for a concerted versus stepwise mechanism in S_NAr reactions can be dependent on the substitution pattern and/or nature of the substrate/nucleophile pair: (a) Liljenberg, M.; Brinck, T.; Herschend, B.; Rein, T.; Tomasi, S.; Svensson M. *J. Org. Chem*. **2012**, *77*, 3262; (b) Fernandez, I.; Frenking,G.; Uggerud, E. *J. Org. Chem*. **2010**, *75*, 2971; (c) Glukhovtsev, M. N.; Bach, R. D.; Laiter, S. *J. Org. Chem*. **1997**, *62*, 4036; (d) Renfrew, A. H. M.; Taylor, J. A.; James M. J. Whitmore, J. M. J.; Williams, A. *J. Chem. Soc. Perkin Trans.* **1993**, *2*, 1703.

16. The TS for **1a** instead involving pyridazinone C=O complexation (analogous to that of **1e**) is found to lie +2.7 kcal/mol higher in energy at the B3LYP/6-31G* level of theory, and may too benefit from a small degree of stabilization between the adjacent, axially-disposed methylene CHs of the morpholine and the triazole 2-N (r(C-H···N) = 2.4 – 2.7 Å.). Please see Supporting Information.
17. The nitrogen atom of an oxazole moiety is the more electronegative heteroatom, as supported by B3LYP/6-31G* electrostatic potential-derived charges (Merz-Kollman scheme, constrained to dipole moment.) For the oxazole molecule: $\chi_{(N)}$ = -0.500 vs. $\chi_{(O)}$ = -0.185 ; for substrate **1k**: $\chi_{(N)}$ = -0.481 vs. $\chi_{(O)}$ = -0.156.
18. The corresponding transition structures (see Supporting Information) involving complexation by the carbonyl and oxazole oxygen atoms lie +2.9 and +4.4 kcal/mol, respectively, above that corresponding to oxazole nitrogen stabilization at the B3LYP/6-31G* level of theory.
19. While S_NAr reactions of substrates **2a-d** may potentially occur via either a concerted or stepwise mechanism, it is generally accepted that in either case, initial addition of the nucleophile to substrates is typically rate limiting (Ref. 9a).
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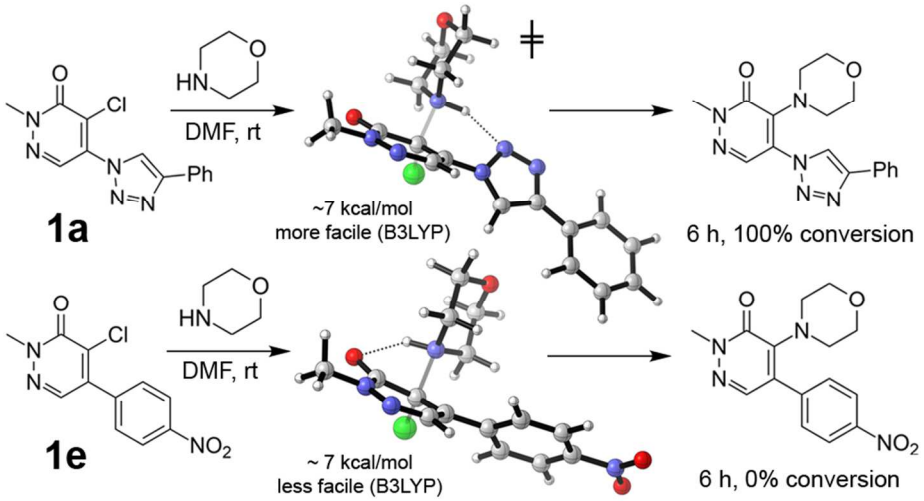
TOC graphic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DMF, rt
Cl
N
N
N
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more facile (B3LYP)
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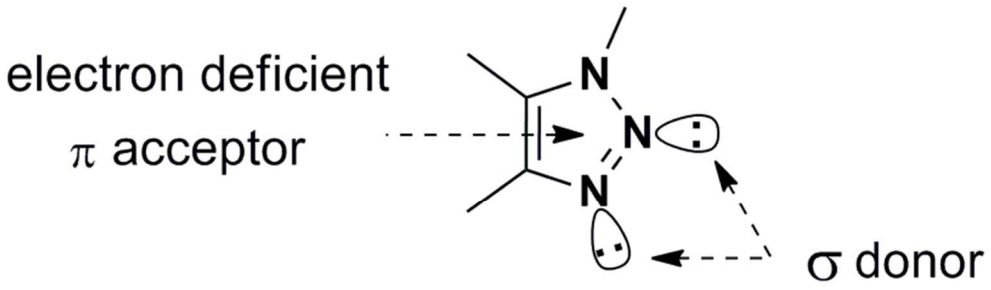

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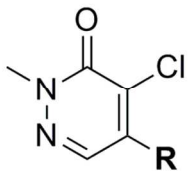
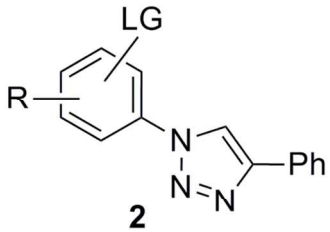


1

R = triazolyl or related (hetero)aryl groups



2

R = other groups

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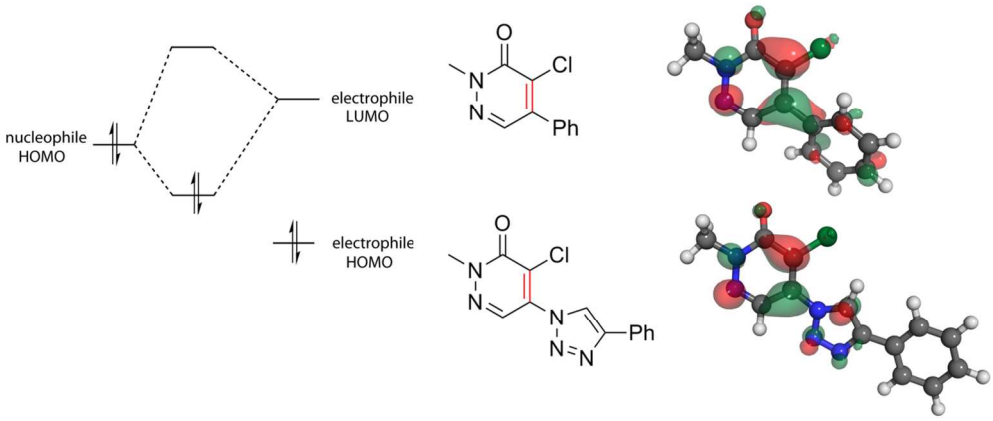

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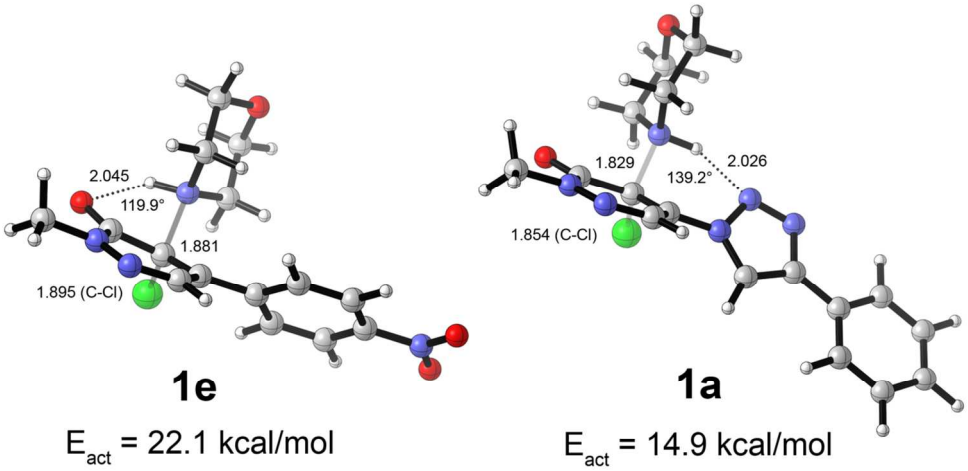

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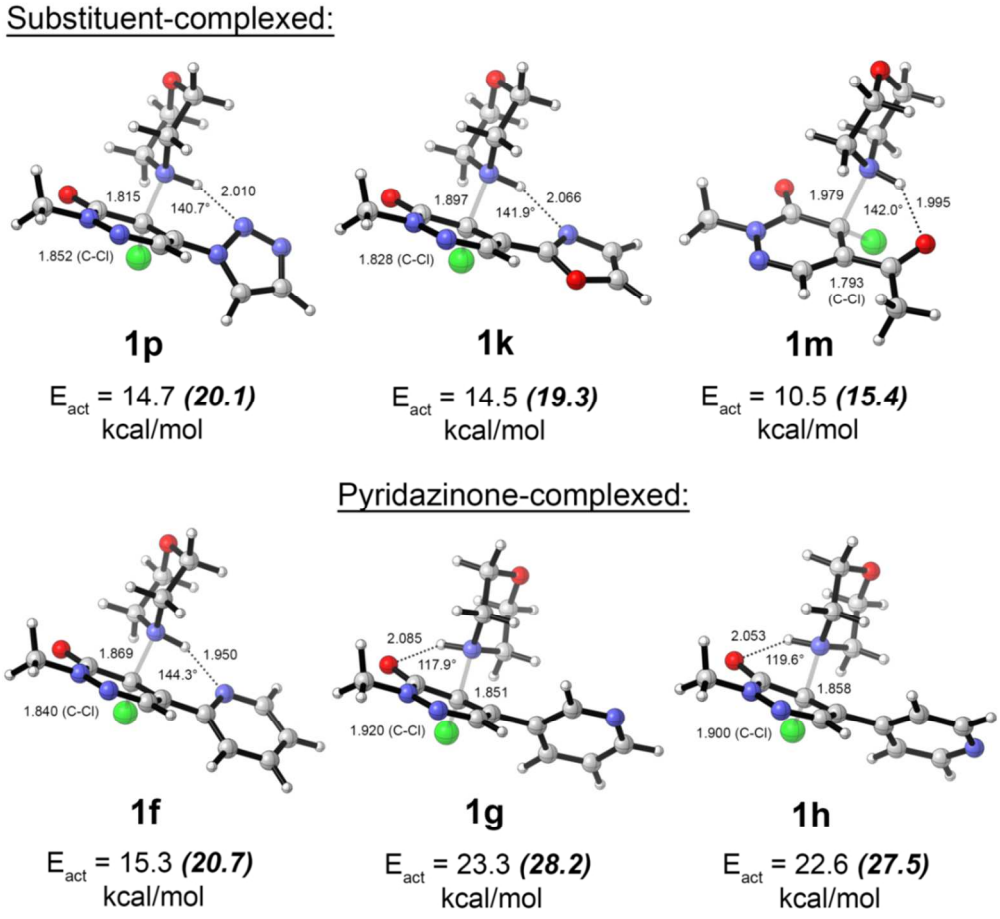

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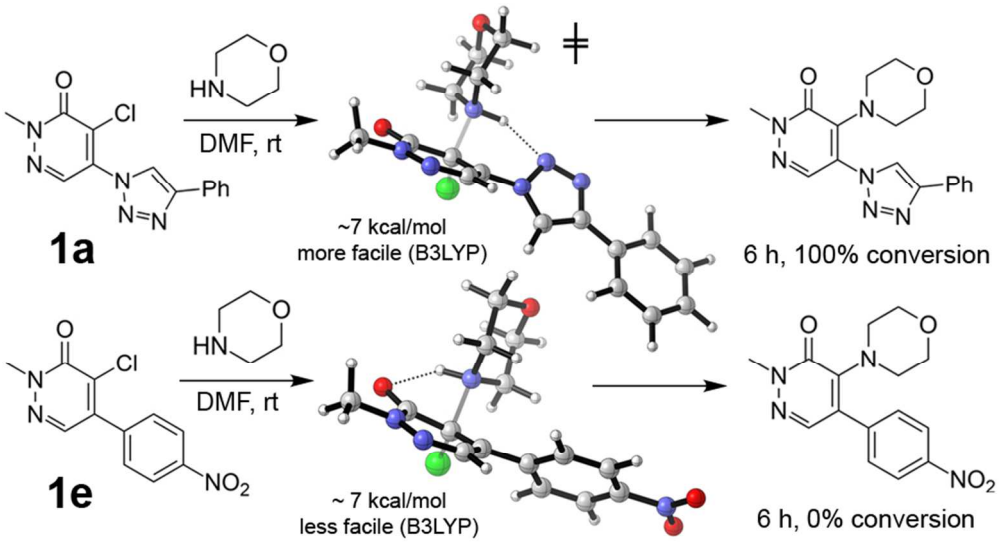

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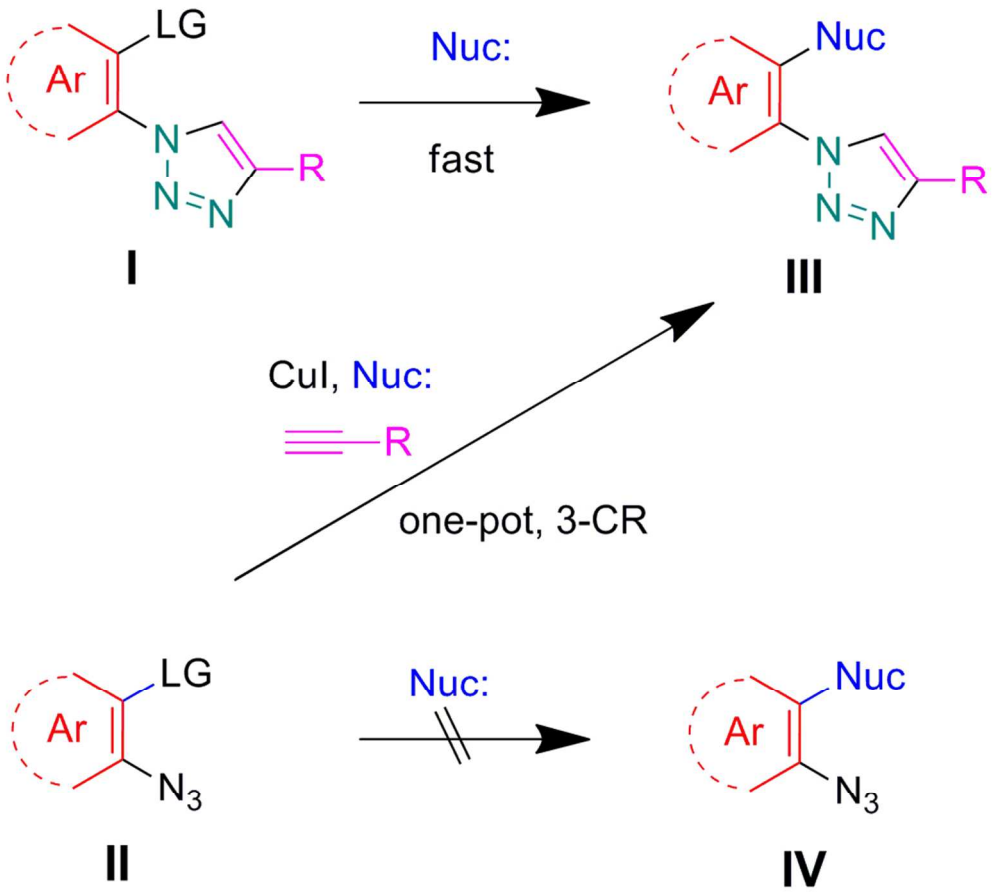

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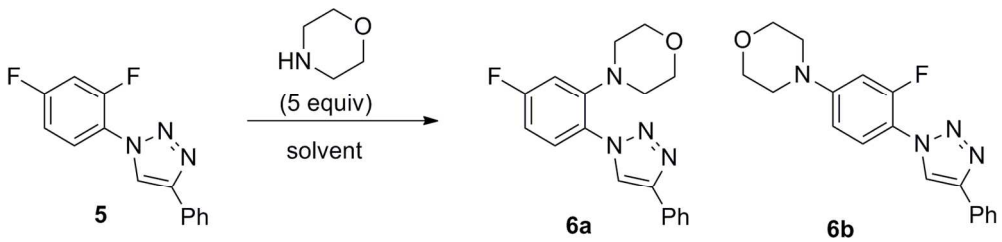

DMSO, 100 °C, 10 h	42%	45%
dioxane, 100 °C, 72 h	73%	5%

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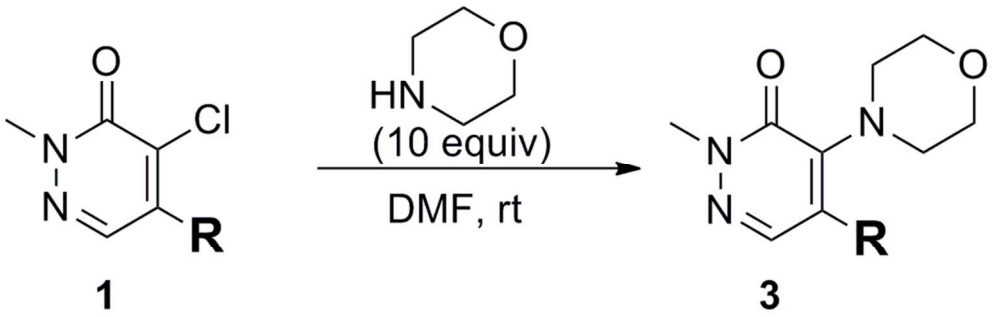

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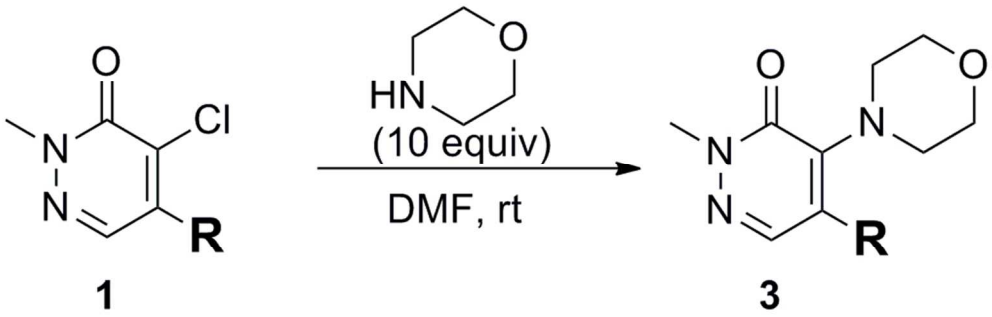

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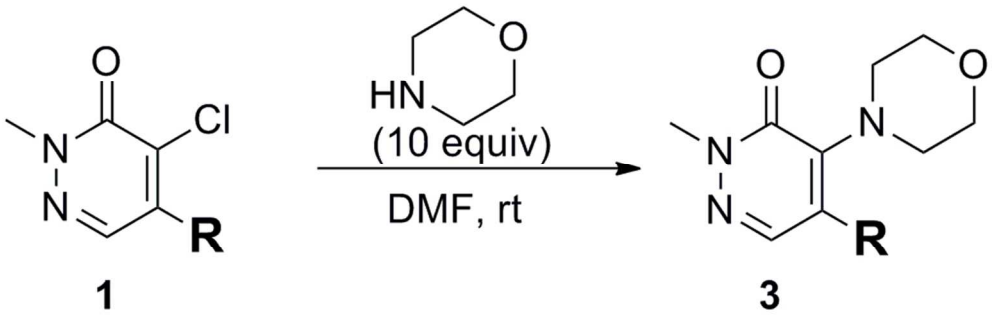

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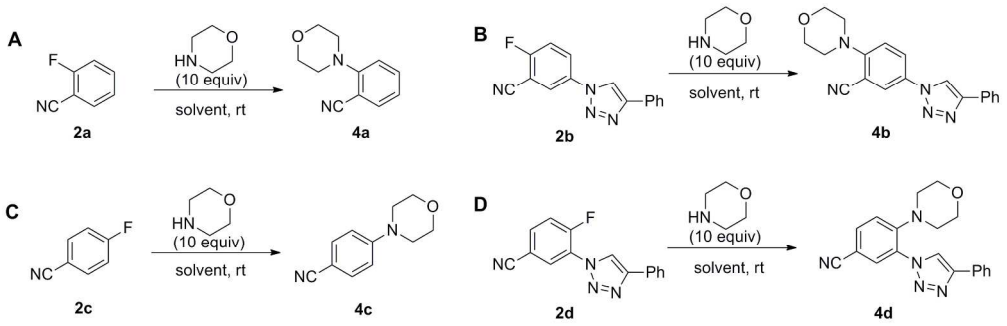

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