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Authors	Valentin Radiupov, Grigory Kantin, Stepan Meshalkin, Elena Tupikina and Dmitry Dar'in
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ORCID® iDs	Valentin Radiupov - https://orcid.org/0009-0002-9662-8259; Grigory Kantin - https://orcid.org/0000-0001-9141-680X; Dmitry Dar'in - https://orcid.org/0000-0002-0413-7413

Blue Light Induced N-H Functionalization of Tetrazoles with Aryldiazoacetates: Access to 1,5-disubstituted Regioisomers

Valentin Radiupov,[a] Grigory Kantin,[a] Stepan Meshalkin,[a] Elena Tupikina,[a] Dmitry Dar'in[a,b] *

[a] Saint Petersburg State University, Saint Petersburg, 199034 Russian Federation

[b] Saint Petersburg Research Institute of Phthisiopulmonology, Saint Petersburg, 191036 Russian Federation

* Corresponding author at: Department of Medicinal Chemistry, Institute of Chemistry, Saint Petersburg State University, 26 Universitetskiy pr., Peterhof 198504 Russian Federation, E-mail address: d.dariin@spbu.ru

Abstract

A novel method for synthesizing 1,5-disubstituted tetrazole derivatives via blue light-promoted N–H insertion of aryldiazoacetates into NH-tetrazoles is presented. The reaction affords mixtures of regioisomeric products, with a predominance of 1,5-disubstituted derivatives. A comprehensive investigation of reaction conditions and substrate effects influencing regioselectivity has been performed. These findings provide new insights into the regioselectivity of NH-tetrazole alkylation and reveal potential applications of this approach in the assembly of tetrazole-containing scaffolds.

Keywords: ***N***-alkylation; diazocarbonyl compounds; N-H insertion reaction; regioselectivity; tetrazoles

Introduction

Among five-membered N-containing heterocycles, the tetrazole ring occupies an important position. In materials science, this nitrogen-rich structural motif is employed to synthesize high-energy compounds. Tetrazoles are also significant scaffolds in medicinal chemistry, serving as bioisosteres of carboxylic acids and amide moieties. Numerous tetrazole-containing compounds are known to exhibit a broad spectrum of biological activities, including antibacterial, antifungal, antitumor, anti-inflammatory, and other pharmacological effects. [1, 2].

One of the key issues associated with modification of the tetrazole ring is the regioselectivity of the *N*-alkylation reaction. Conventional alkylation variants generally yield mixtures of two regioisomers with a predominance of N(2)-alkylated (2,5-disubstituted) product. These methods include alkylation with alcohols and alkenes under acidic catalysis, alkyl halides under basic conditions, alcohols via the Mitsunobu reaction, diazomethane, and *N*-tosylhydrazones. [3-14].

At the same time, examples of regioselective synthesis of N(1)-substituted tetrazoles in the literature are scarce. Conversely, 1,5-disubstituted tetrazole motifs are prominent in several

biologically active compounds (Figure 1). For example, compound **1** is active against *Candida* spp., *Criptococcus neoformance*, and *Aspergillus* spp. Peptidomimetic **2** is a bioisosteric analog of the known HIV protease inhibitor Saquinavir (Invirase). Compound **3** exhibits cytostatic activity *in vitro* toward several tumor cell lines. Well-known drugs include Corazolum (Cardiazol, **4**), which has been used for a long time as an anticonvulsant and a central nervous system stimulant, and Cilostazol (Platal, **5**), which is used in patients with peripheral ischemia to relieve the symptoms of intermittent claudication [15]. Thus, the development of new methods for obtaining 1,5-disubstituted tetrazole derivatives remains an important task in organic chemistry.

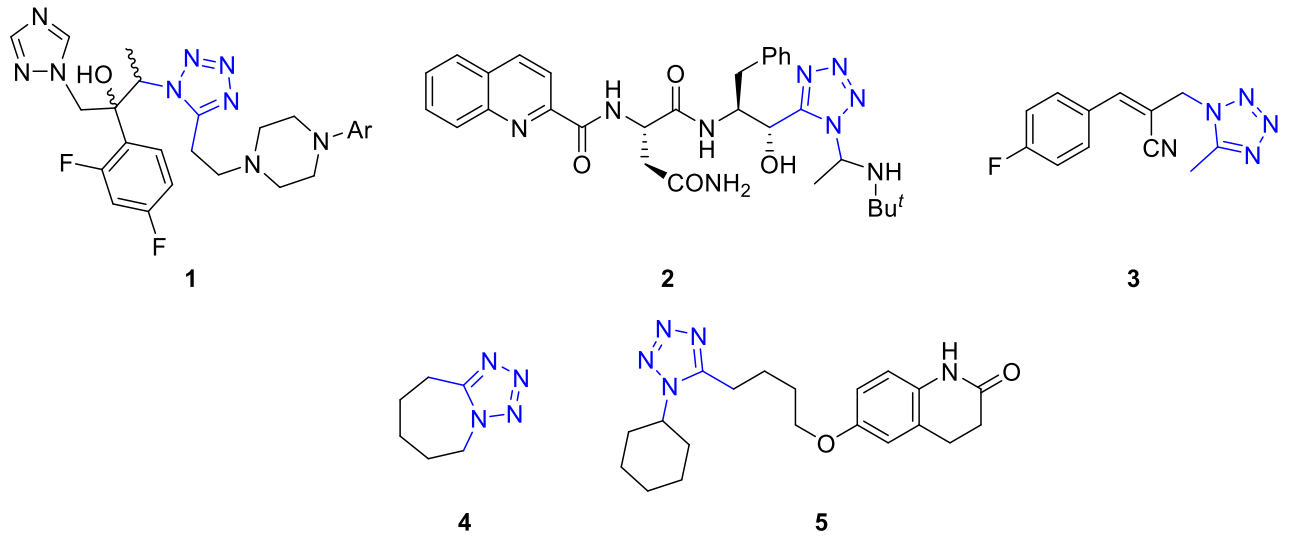
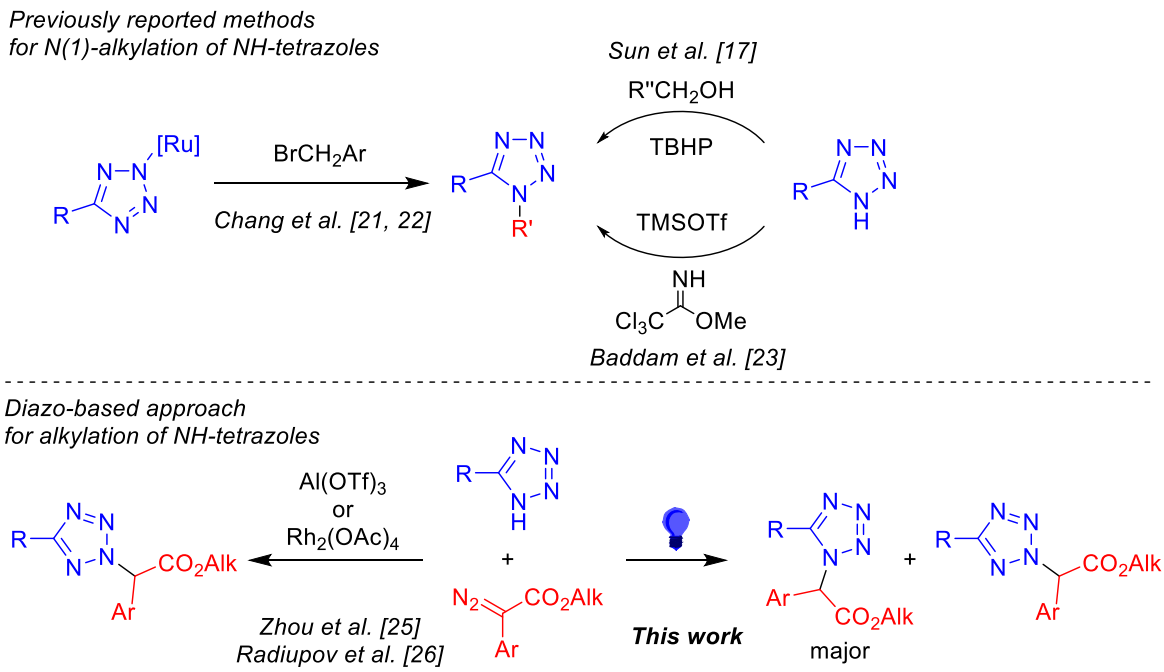


Figure 1. Biological active compounds containing 1,5-disubstituted tetrazole

One such method involves the exhaustive alkylation of 2,5-disubstituted tetrazole [16, 3]. Several azoles were reacted with ethanol in the presence of *tert*-butyl hydroperoxide to afford the corresponding α-(tetrazol-1-yl)-substituted ethers [17]. Thus, 1,5-disubstituted tetrazoles were obtained with good yields, including those bearing electron-acceptor substituent in the side chain. Few studies have reported that the use of boron trifluoride etherate as an additive during alkylation with allylic/propargylic alcohols [18, 19], as well as throughout benzylic C–H bond cross-coupling, leads to an increased formation of the N(1)-modified regioisomer [20]. Additionally, alkylation products at the N(1)-position were also obtained from the ruthenium tetrazole complex [21, 22]. Tetrazoles were methylated at the N(1)-atom with high regioselectivity using methyl 2,2,2-trichloroacetimidate [23] (Scheme 1). However, overall, it can be noted that the available methods for selective N(1)-modification of tetrazoles are quite limited, typically relying on very specific tetrazole substrates or alkylating agents.



Scheme 1. Selected examples of N-modification of NH-tetrazoles.

Recent studies have demonstrated that diazocarbonyl compounds can serve as effective reagents for regioselective modification of NH-tetrazoles. Previously, Zhao and colleagues showed that the N–H insertion reaction of aryldiazoacetates into benzotriazoles, catalyzed by $B(C_6F_5)_3$, affords high yields of N(1)-substituted benzotriazoles [24]. This reaction successfully enabled the selective modification of an unsubstituted tetrazole at the N(1) position, with a yield of 64%. More recently, it has been shown that the N–H insertion reaction of diazo compounds, catalyzed by $Al(OTf)_3$, allows the preparation of N(2)-derivatives with high regioselectivity [25]. Almost simultaneously, we demonstrated that catalysis by Rh(II) complexes also enables this transformation with high regioselectivity [26]. All these approaches are illustrated in Scheme 1.

The regioselectivity of tetrazole alkylation by diazo compounds is influenced by a variety of factors. First, it is essential to determine whether the tetrazole reacts in its neutral or anionic form. In the case of the neutral form, the position of the tautomeric equilibrium between the 1H- and 2H-tautomers also contributes to regioselectivity. Additionally, the properties of the reaction medium and the nature of the substituent at the C5 carbon atom should be considered [6]. A recent study attempts to explain the regioselectivity of tetrazole alkylation in terms of the reaction mechanism (SN1 or SN2), utilizing the diazotization of amines to generate the alkylating agent [27]. It was shown that reactions likely proceeding via an S_N2 mechanism exhibit higher regioselectivity compared to those proceeding via an S_N1 mechanism. Surprisingly, steric factors do not have a decisive influence on the regioselectivity of the reaction.

An intriguing method for modifying the tetrazole ring with diazo compounds involves conducting the reaction under blue light photolysis conditions. Recent advances in visible-light-mediated diazo chemistry have demonstrated significant advantages over classical methods for generating reactive carbene intermediates. For instance, LED-induced reactions proceed at lower temperatures compared to thermolysis and enable the avoidance of expensive transition metal catalysts, which can also pose environmental risks. [28-32]. Moreover, the use of visible light in the chemistry of diazo compounds opens up new reaction pathways previously unknown in classical metallocarbene chemistry, for instance, by altering the chemoselectivity [33, 34]. Photoinduced N-H insertion of aryl diazoacetates is known for amines, amides, anilines, sulfonamides, isatins, and imides. Among N-heterocycles, insertion reactions have been described for carbazoles, indoles, pyrazoles, and triazoles [35-38]. In a recently published study, selective N(1)H-insertion into benzotriazole was achieved via blue light irradiation (λ = 425 nm) in the presence of *p*-benzoquinone and *tert*-butyl nitrite as additives [39]. The authors propose that irradiation generates a more stable N(1)-radical of benzotriazole, which subsequently reacts with a free carbene to afford the N(1)H-insertion product. This work highlights the significance of employing blue light as an alternative to transition metal catalysis, since under Rh(II) catalysis, diazo compounds predominantly yield N(2)-substituted benzotriazoles with high regioselectivity [40]. Notably, the use of blue light led to a switch in the regioselectivity of the N–H insertion reaction from the N(2)- to the N(1)-atom.

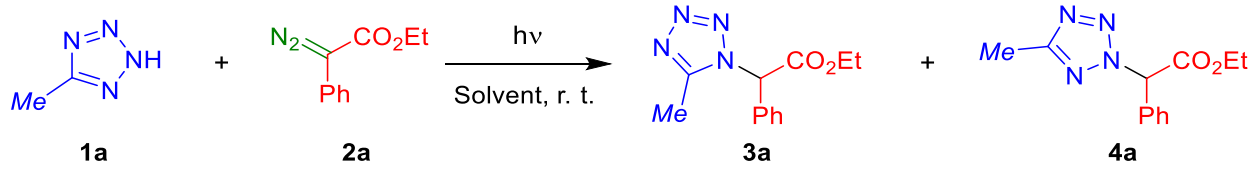
During the optimization of the alkylation reaction conditions described in our previous work [26], we discovered that the N–H insertion reaction of a diazo compound into a tetrazole, initiated by blue light, affords a higher yield of the N(1)-regioisomer (Scheme 1). Given that the development of new methods for modification of the tetrazole ring at the N(1) position remains a significant challenge in tetrazole chemistry, we undertook a detailed study of the factors influencing the regioselectivity of this transformation and evaluated its synthetic potential for the preparation of N(1)-substituted tetrazole derivatives.

Results and discussion

Our first experiment involving tetrazole **1a** and diazo reagent **2a**, which demonstrated predominant formation of the N(1)-alkylated regioisomer **3a** with both high conversion and overall yield, was conducted using a standard inert solvent commonly employed for such transformations – DCM (Table 1, Entry 1). It is well established that solvent properties, such as polarity, influence the tautomeric equilibrium of tetrazole forms [41, 42], and the regioselectivity of the reaction, in turn, can depend on it. Therefore, the model reaction was carried out in various solvents in order to reveal a change in the ratio of regioisomeric reaction products in favor of the N(1)-regioisomer. Phenyl diazoacetate **2a** serves as a convenient substrate because it absorbs visible light efficiently over a

broad wavelength range of 400–500 nm, facilitating its photodecomposition [43]. As seen from Table 1, none of the solvents contributed to increasing the content of the N(1)-regioisomer in the reaction mixture. The use of 1,4-dioxane (Entry 5) led to an unexpected effect, which consisted in the inversion of the ratio and yields of regioisomeric reaction products.

Table 1. Optimization of blue light-promoted N-H insertion reaction conditions.[a, b]



1a **2a** **3a** **4a**

Entry	Solvent	NMR ratio	NMR yield (%)	
		3a/4a	**3a**	**4a**
1	DCM	62:38	49	30
2	EtOAc	57:43	31	22
3	Toluene	55:45	9	8
4	MeCN	61:39	35	23
5	1,4-dioxane	31:69	19	41
6	Et_2O	55:45	27	22
7	THF		trace	
8	DMSO		n/a	
9	DMF		n/a	
10	PhCl	58:42	21	15
11	$CHCl_3$	59:41	19	13
12	15 mol% PBQ, 20 mol% TBN, DCM	52:48	31	28
13	10% K_3PO_4, DCM	61:39	48	31
14[c]	BF_3 10 mol%, DCM	49:51	26	27

[a]Reactions were run with 0.20 mmol of **1a**, 0.24 mmol of **2a**, and 0.8 mL of the solvent. [b]The yields and regioisomeric ratios were estimated from the ^{1}H NMR spectra of the reaction mixtures using 2,4-dinitrotoluene as an internal standard. [c]Reaction was run in the dark.

Sulfoxonium ylides formed from the photodecomposition of diazo compounds in DMSO upon visible light irradiation are capable of undergoing subsequent formal insertion into X–H bonds [44-46]. The reaction of photolytic O-H insertion in DMF medium is also described [47]. Hence, we also tested these highly polar aprotic solvents (DMSO, DMF), which are not typically used in reactions involving carbenes. However, these attempts were unsuccessful (Entries 8-9).

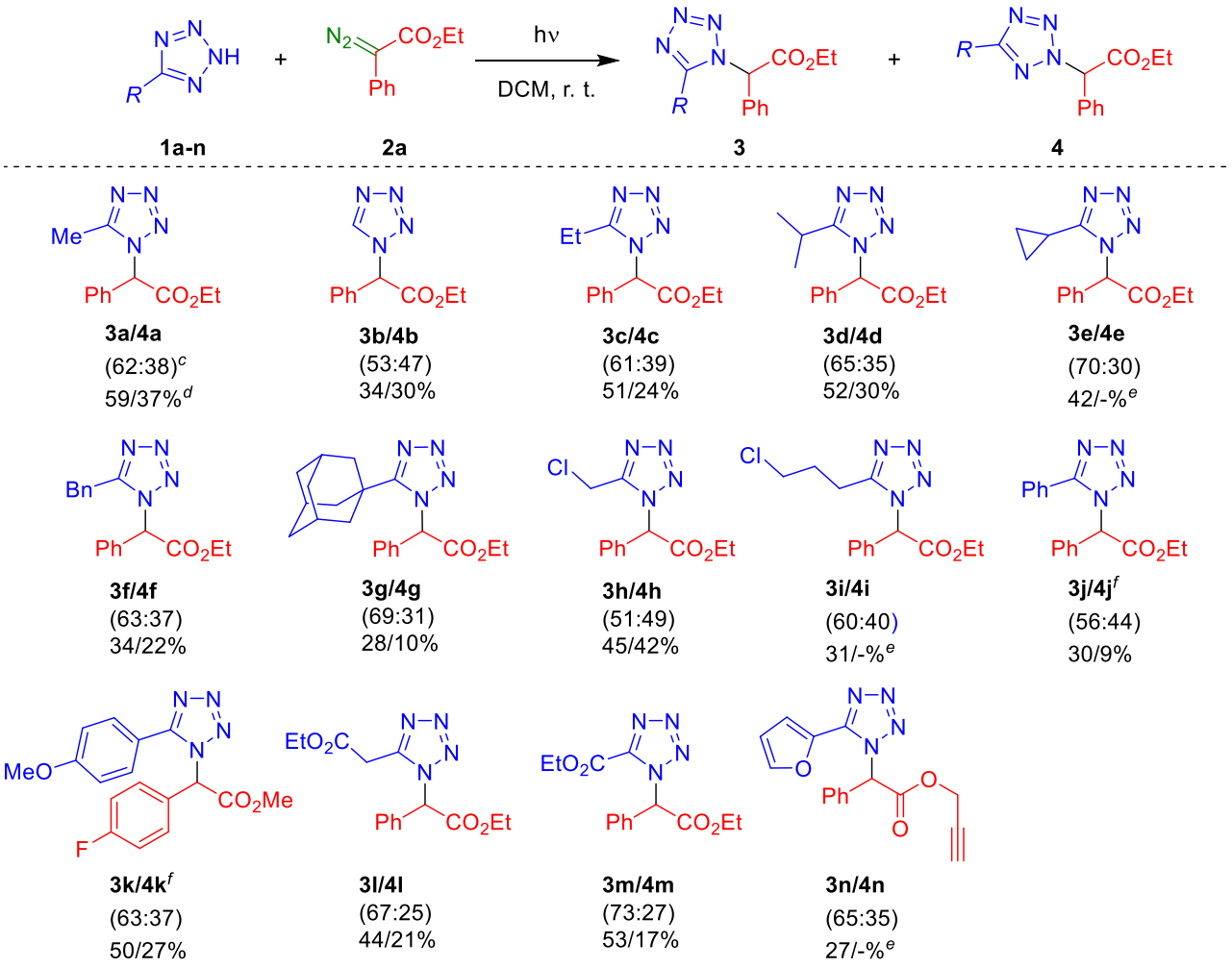
We then explored other approaches to alter the ratio of regioisomeric products. For example, photolysis in the presence of radical initiators is known to promote selective formation of N(1)-regioisomer derivatives of benzotriazole [39]; however, this approach proved ineffective in our system. Similarly, addition of catalytic amounts of base [36, 37] or Lewis acid did not enhance selectivity.

We then implemented an alternative strategy that involved blocking the N(2)-atom with a suitable protecting group, which theoretically could statistically favor an increased formation of N(1)H-insertion products [48]. Additionally, from the reviews cited above, exhaustive alkylation of 2,5-disubstituted tetrazoles results in the formation of 1,5-disubstituted derivatives [3, 6]. However, when N(2)-Boc and N(2)-Tr protected tetrazoles were introduced into the reaction with diazo reagent **2a**, upon full conversion of the diazo compound, the anticipated reaction products were not observed.

It is noteworthy that during the optimization experiments no significant influence of the starting materials ratio was observed. The best result was achieved for entry 1 using 1.2 equivalents of diazo reagent **2a**.

Following the optimization of reaction conditions, various tetrazoles were systematically introduced into the reaction with phenyl diazoacetate **2a**, with deliberate variation of the steric and electronic properties of the substituent at the C-5 position (Scheme 2). The results indicate that the ^{1}H NMR-measured ratio of *N*-alkylated regioisomers **3** and **4** does not change significantly. At the same time, it is difficult to establish a clear pattern of influence on the yields of reaction products. Tetrazoles bearing sterically hindered adamantyl and phenyl substituents provide comparable yields (compounds **1g** and **1j**), although the regioisomeric ratio remains approximately constant relative to sterically unhindered substrates. Phenyl tetrazole **1j** and *p*-methoxyphenyl tetrazole **1k** were reacted in acetonitrile due to the critical issue of their low solubility in dichloromethane, which adversely affected the formation of the insertion reaction products. The noted trends in the yield patterns of reaction products correlate well with the previously published similar reaction for 1,2,3-triazoles – the regioselectivity of the reaction changes minimally with varying steric factor [37].

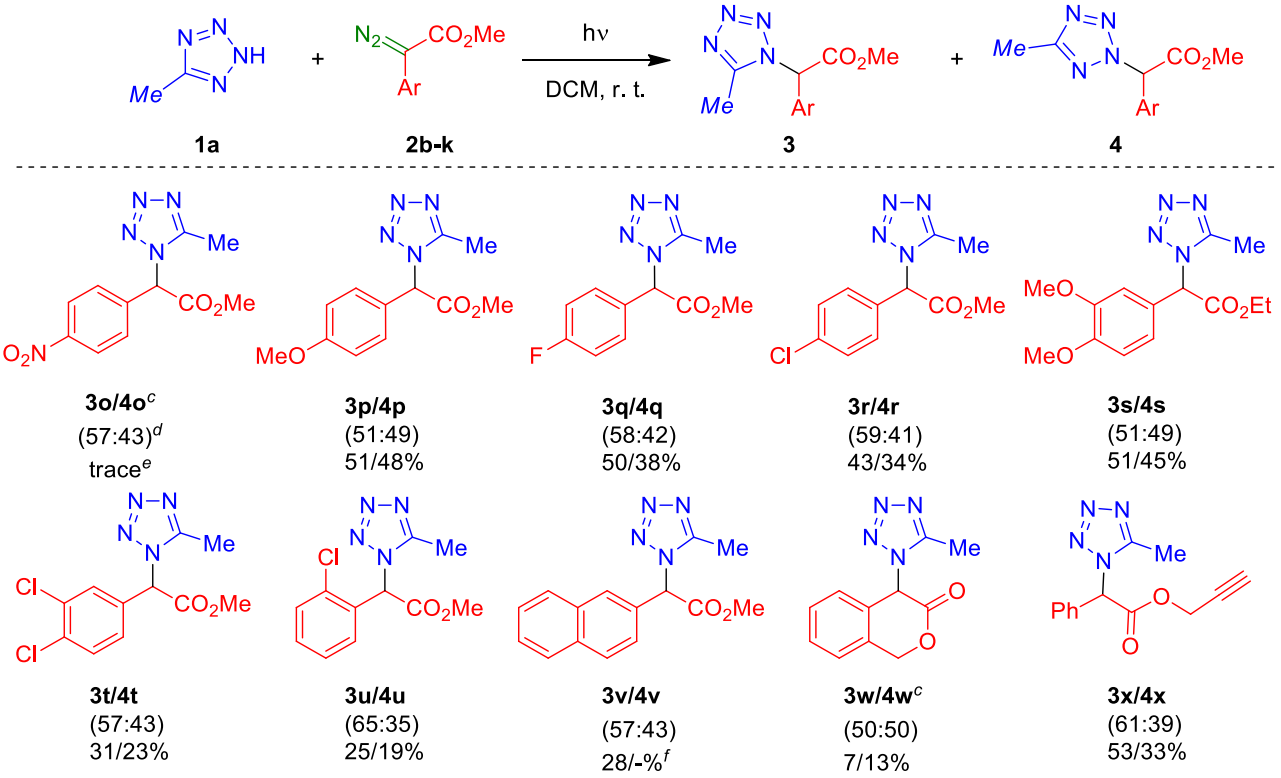
The reaction of tetrazol-5-carboxylate **1m** affords yields of products **3m** and **4m** comparable to those observed in the previously described reaction proceeding without initiation [26], suggesting ambiguity in the underlying reaction mechanism. It should be noted that the ester group in compound 1m may exert a specific directing effect, preferentially guiding the alkylating electrophile to the N(1)-position [49]. Interestingly, in the case of unsubstituted tetrazole **1b**, an equal regioisomeric ratio and comparable yields of the regioisomeric products **3b** and **4b** are observed.



Scheme 2. Scope of NH-tetrazoles. [a]Reactions were run with 0.5 mmol of **1**, 0.6 mmol of diazo reagent **2a**, in 2.0 mL of DCM at r. t. under blue light irradiation. [b]Major regioisomer is shown. [c]NMR ratio of regioisomers. [d]Isolated yields of regioisomers. [e]Minor regioisomer was not isolated. [f]Reaction was performed in acetonitrile.

Then, various diazo reagents were introduced into the reaction with 5-methyl-1*H*-tetrazole **1a** (Scheme 3). Shifting from electron-withdrawing substituents to electron-donating on the benzene ring of diazo compound **2** leads to an increase in the yields of both regioisomeric products, while the NMR-measured regioisomeric ratio stays relatively stable. For instance, only trace amounts of products **3o/4o** were observed for *p*-nitrophenyl diazoacetate **2b** (the numbering of the diazo reagents corresponds to that given in the Supporting Information File 1), whereas the unsubstituted phenyl diazoacetate **2a** (products **3a/4a**), halogen-substituted compounds **2d** and **2e** (products **3q/4q** and **3r/4r**), and methoxy derivatives **2c** and **2f** (products **3p/4p** and **3s/4s**) afforded higher yields of alkylated products. Incorporation of *ortho*-substituents (compound **2h**, products **3u/4u**), as well as the use of the naphthyl derivative **2i** (products **3v/4v**), decreases the overall yield. The use of the cyclic analogue **2j** results in an extremely low yield, which is consistent with literature data on the use of this substrate in photolytic reactions [50] and may therefore indicate hampered carbene formation or its instability. The reactivity of aryldiazoacetates **2** varies depending on the nature of the

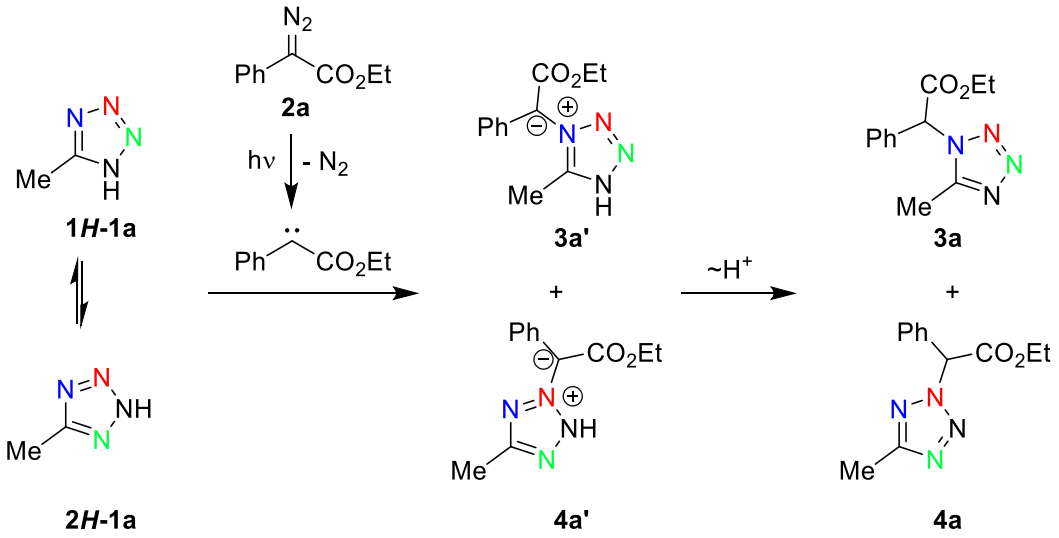
substituent on the benzene ring, generally similar to the examples reported in previously published works [37, 50].



Scheme 3. Scope of diazo reagents. [a]Reactions were run with 0.5 mmol of **1a**, 0.6 mmol of diazo reagent **2**, in 2.0 mL of DCM at r. t. under blue light irradiation. Isolated yields of regioisomers are indicated. [b]Major regioisomer is shown. [c]Reaction was carried out for 72 h. [d]NMR ratio of regioisomers is given in parentheses. [e]Was not isolated. NMR yield is less than 10%. [f]Minor regioisomer was not isolated.

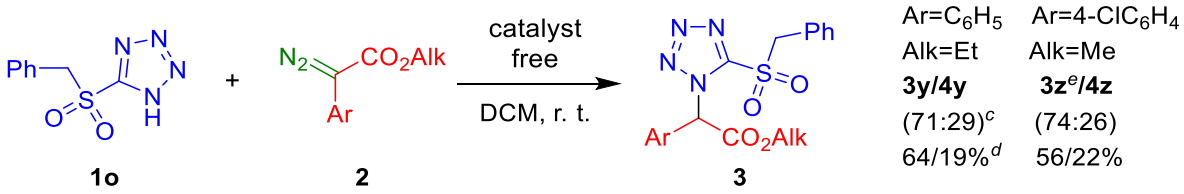
To rationalize the observed regioselectivity of the N–H insertion reaction, we performed quantum chemical calculations (for details, see Supporting Information File 1). Each tautomeric form of tetrazole contains three nonequivalent nitrogen atoms capable of acting as nucleophilic sites for attack on the electrophilic carbene. Assuming that the reaction proceeds via an ylide mechanism, we calculated the energies of six intermediate ylides — three ylides with pyridine-type nitrogen atoms of the 1*H*-tautomer (*N*2, *N*3, *N*4) and three ylides with pyridine-type nitrogen atoms of the 2*H*-tautomer (*N*1, *N*3, *N*4). It turned out that intermediates **3a'** and **4a'** are energetically preferable in the case of the formation of isomers **3a** and **4a**, respectively (Scheme 4). Consequently, the reaction most likely proceeds through the formation of intermediates **3a'** and **4a'**. Furthermore, intermediate **3a'** is lower in energy than **4a'**; for this reason, under thermodynamic control conditions, the product **3a** will predominate in the reaction mixture, which is in agreement with our experimental observations (**3a**:**4a** as 62:38). It is significant to point out that, in our calculations, we did not take into account the quantitative ratio of the tautomeric forms of the starting tetrazole **1*H*-1a** and **2*H*-1a**, as this ratio is dynamic with very rapid interconversion between forms and is difficult to reliably assess. However,

the N-H acidity (pKa) of tetrazoles is comparable to that of the carboxyl group [41]; therefore, a reaction mechanism involving protonation of the forming carbene cannot be excluded. [34].



Scheme 4. Plausible reaction mechanism. [a]Only the most energetically favorable ylides **3a'** and **4a'** are shown. For details see Supporting Information File 1.

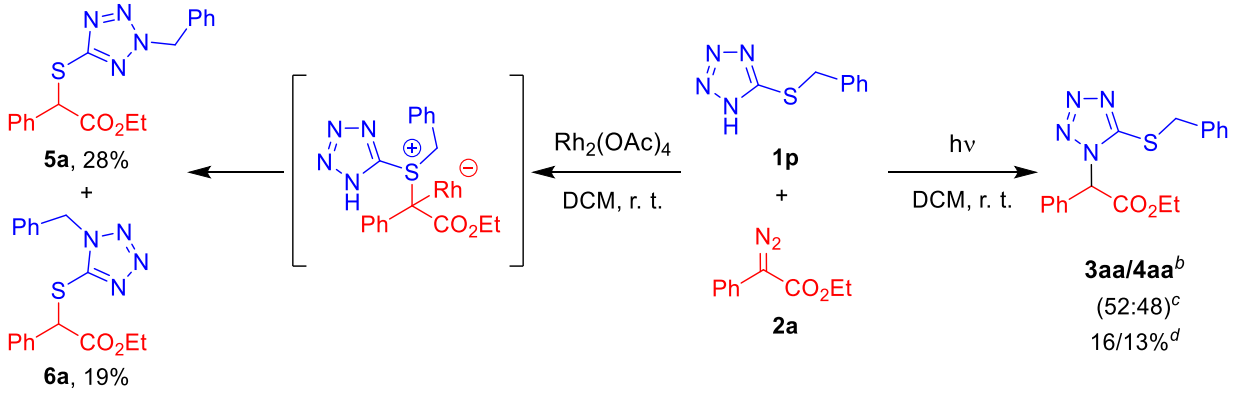
In our previous work, we found that the reaction with tetrazol-5-carboxylate **1m** proceeds under conditions without external initiation, leading to the formation of regioisomers **3m** and **4m** with yields of 60% and 18%, respectively. The introduction of a strongly electron-withdrawing substituent such as a sulfonyl group into the tetrazole ring (compound **1o**, R=SO_2Bn) also enabled the reaction to proceed without initiation by light irradiation (Scheme 5).



Scheme 5. Catalyst free N-H insertion reaction. [a]Reactions were run with 0.5 mmol of **1o**, 0.6 mmol of diazo reagent **2**, n 2.0 mL of DCM at r. t. in the dark. [b]Major regioisomer is shown. [c]NMR ratio of regioisomers. [d]Isolated yields of regioisomers. [e]Single-crystal X-ray analysis data were obtained (see Supporting Information File 1).

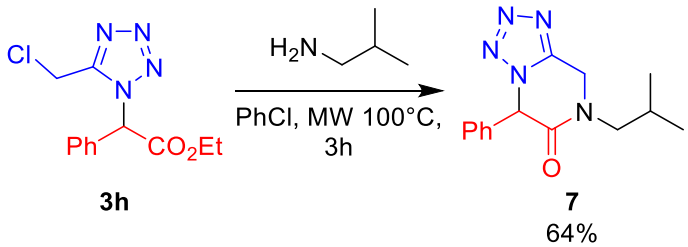
As in the case of **1m**, the regioselectivity of the reaction shifts towards the formation of N(1)H-insertion products **3y** and **3z**, which is evident both from the NMR ratio and the isolated yields. The products **3y/4y** were also obtained under blue light irradiation with 58% and 24% yield, respectively (NMR ratio 72:28). The example of obtaining compounds **3y/4y** and **3m/4m** shows that initiation by photolysis somewhat decreases the yield compared to the reaction variant with no light irradiation. Apparently, due to the increased N-H acidity of tetrazole, the reaction proceeds by an alternative mechanism through protonation of the initial diazo compound.

The reaction of phenyl diazoacetate **2a** with compound **1p** (R=SBn) led to an unexpected result. Using blue light, we obtained insertion products into the N-H bond of the tetrazole **3aa/4aa** (Scheme 6). The same product was previously obtained under aluminum triflate catalysis [25]. However, when rhodium tetraacetate was used as the catalyst, we isolated the rearrangement products **5a/6a** (NMR ratio 69:31), for which we observed the ^{15}N-^{1}H correlation of the methylene group instead of the characteristic correlation of the methine group. Several documented rearrangements of sulfur ylides are reported in the literature [51–53], including the migration of the benzyl fragment. We propose that this chemoselectivity can be explained using the HSAB (Hard and Soft Acids and Bases) theory. The free carbene, acting as a harder electrophile, preferentially attacks the harder nitrogen atom of the tetrazole ring, whereas the rhodium-bound carbene favors the sulfur atom for ylide formation.



Scheme 6. *N/S* chemoselectivity in ylide formation. [a]Reactions were run with 0.5 mmol of **1p**, 0.6 mmol of diazo reagent **2a**, n 2.0 mL of DCM at r. t. using 1 mol % of $Rh_2(OAc)_4$ or under blue light irradiation. [b]Major regioisomer is shown. [c]NMR ratio of regioisomers. [d]Isolated yields of regioisomers.

The 1,5-disubstituted tetrazoles obtained by our method are convenient precursors for the synthesis of bicyclic structures with a fused tetrazole ring. The reaction of **3h** with isobutylamine allowed us to obtain product **7** in good yield (Scheme 7).



Scheme 7. Cyclocondensation of **3h** with amine to give bicyclic derivative **7**.

Conclusions

In this study, we present a novel method for modifying the tetrazole ring to synthesize 1,5-disubstituted derivatives using diazo compounds under blue light irradiation. The canonical pattern

of regioselectivity was successfully altered to favor N(1)-alkylation; however, the underlying reasons for this selectivity remain unclear. Notably, switching the chemoselectivity of ylide formation was achieved by transitioning from Rh(II) catalysis to visible-light activation. Additionally, we observed that tetrazoles with increased NH acidity undergo insertion reactions with diazo compounds without the need for external initiation.

Although the use of blue light does not confer high regioselectivity in the reaction, this approach nevertheless enables the isolation of N(1)-substituted tetrazole derivatives in pure form with moderate yields, which is often a challenging task. To date, only a very small number of specific methods exist for the selective N(1)-modification of tetrazoles. Additionally, this methodology opens up possibilities for various intramolecular cyclizations aimed at synthesizing fused tetrazole ring systems with potential biological activity. Furthermore, replacing heavy metal complexes with visible-light activation broadens the scope of applications, particularly in pharmaceutical synthesis. Moreover, the generation of free carbenes under blue light irradiation is suitable for further mechanistic studies of reactions involving diazo compounds [54]. Finally, this work provides insights to the active discussion of regioselectivity in NH-tetrazole alkylation.

ASSOCIATED CONTENT

Data Availability Statement

All data that supports the findings of this study is available in the published article and/or the supporting information of this article.

Supporting Information File 1

See the Supporting Information for full experimental information, computational details, X-ray crystallographic data, synthetic procedures, analytical data and NMR spectra for the reported compounds.

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ORCID® iDs

Valentin Radiupov - https://orcid.org/0009-0002-9662-8259

Grigory Kantin - https://orcid.org/0000-0001-9141-680X

Stepan Meshalkin - https://orcid.org/0000-0002-5384-0703

Elena Tupikina - https://orcid.org/0000-0002-0998-8348

Dmitry Dar'in - https://orcid.org/0000-0002-0413-7413

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