EurJOC
European Journal of Organic Chemistry

Research Article
doi.org/10.1002/ejoc.202401138

Chemistry Europe
European Chemical Societies Publishing

www.eurjoc.org

Facile *N*-Modification of NH-Tetrazoles via Rh(II)-Catalyzed N–H Insertion Involving Structurally Diverse Diazo Reagents

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A convenient method for the *N*-modification of NH-tetrazoles by the Rh(II)-catalyzed insertion reaction of diazocarbonyl compounds into the N–H bond has been proposed. A wide range of structurally diverse diazo reagents (including heterocyclic ones) as well as tetrazoles with different substituents in the fifth position have been used to prepare 2,5-disubstituted tetrazole derivatives in good and high yields and with high regioselectivity. It is shown that the regioselectivity of the reaction can decrease in the presence of electron withdrawing groups in the tetrazole, as well as in the presence of protic acids.

Introduction

The importance of tetrazoles in modern chemical science and industry can hardly be overestimated. First of all, the role of this unique heterocycle in the field of medicinal chemistry and drug development is enormous, where the tetrazole cycle is undoubtedly one of the privileged scaffolds. Suffice it to say that tetrazole is among the most frequently occurring *N*-heterocyclic fragments in molecules of FDA approved pharmaceuticals.[1] The tetrazole ring is actively used in drug design as a bioisosteric replacement, primarily for the carboxyl group,[2] but also for amide moieties.[3] Tetrazole derivatives exhibit a wide range of different biological activities and have numerous therapeutic applications.[4] Of particular note is their importance in the field of anticancer[5] and antidiabetic[6] agents, as well as among medications for the treatment of neurological disorders.[7]

When it comes to specific molecules, the following important FDA-approved drugs can be mentioned (Figure 1): **Valsartan** (trade name Diovan), angiotensin II receptor blocker (ARBs) used to treat high blood pressure, heart failure, and diabetic kidney disease (its analogues with a similar spectrum of action are **Irbesartan** and **Olmesartan**);[8] **Oteseconazole** (brand name Vivjoa), an orally bioavailable and selective inhibitor of fungal cytochrome P450 enzyme 51 (CYP51), showing efficacy in the treatment of recurrent vulvovaginal candidiasis (RVVC);[9] **Tedizolid** (brand name Sivextro), often used as its phosphate ester prodrug (**Tedizolid phosphate**), is an oxazolidinone-class antibiotic for the treatment of acute bacterial skin and skin structure infections (complicated skin and skin-structure infections (cSSSIs));[10] **Cilostazol** (brand name Pletal), a medication used to help the symptoms of intermittent claudication in peripheral vascular disease;[11] **Cenobamate** (brand names Xcopri (US) and Ontozry (EU)), a drug for the treatment of partial-onset seizures, a kind of epilepsy;[12] **Ceforanide**[13] and **Cefotiam**[14] are second- and third-generation cephalosporin antibiotics, effective against many Gram-positive and Gram-negative bacteria, including Escherichia coli, Klebsiella, Enterobacter and Proteus, and most strains of Salmonella, Shigella, Hemophilus, Citrobacter and Arizona species.

Of course, there are many more approved drugs containing the tetrazole moiety. Using the above structures as an example, we wanted to emphasize that among them (as well as other biologically active tetrazole-based molecules) both 1-*N*- and 2-*N*-substituted derivatives are often found along with *N*-unsubstituted ones.

In addition to their utility in medicine, tetrazole derivatives occupy an important place in other fields of science. Tetrazoles are used to produce high-energy materials,[15] they are actively employed in organic synthesis, e.g. as sources of alkylidene carbenes[16] and building blocks for constructing discrete and polymeric assemblies.[17]

Considering the above and the high demand for tetrazole derivatives, an important task is to expand their chemical space and thus develop methods to obtain new diverse structures based on this heterocyclic scaffold. The synthesis and modifications of tetrazoles has been the subject of many review articles dealing with the synthetic approaches known to date.[18] In addition to approaches involving the assembly of the tetrazole ring, methods of introducing substituents into the heterocycle occupy an important place. As far as the modification of nitrogen atoms is concerned, these are mainly *N*-alkylation and *N*-arylation reactions carried out according to various classical or modern procedures.

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202401138

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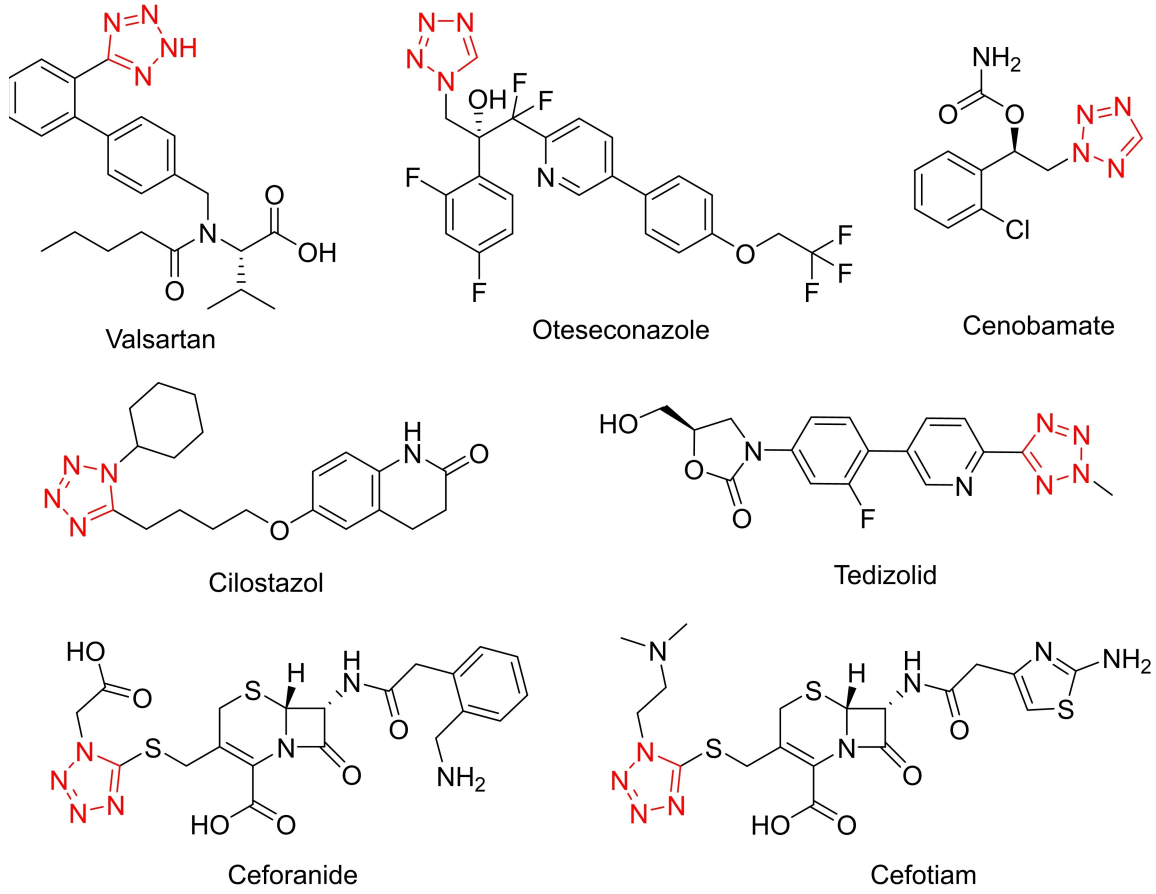

Figure 1. FDA approved tetrazole based drugs.

One of the methods for alkylation of NH-heterocycles is the interaction with diazo reagents,[19] which allows the introduction of fragments of diverse structure with substituents of different nature under mild conditions (catalysis or photolysis) without the use of basic media. To our surprise, this powerful tool for introducing substituents to the nitrogen atom of tetrazoles via diazo chemistry was, until recently, represented in the literature only by isolated examples of *N*-methylation of tetrazole derivatives under the action of diazomethane or its TMS-analogue.[20] We were keen to fill this gap and study in detail the interaction of NH-tetrazoles with various diazocarbonyl (including diazo heterocyclic) reagents to complement the set of known 'classical' *N*-alkylation methods.

It should be noted that during the writing of this paper, the publication by S. Gu and co-workers describing the use of aryldiazoacetates and diazoketones for the regioselective alkylation of tetrazoles under aluminium triflate catalysis was published.[21] Our work complements these studies by suggesting a wider range of diazo reagents suitable for *N*-modification of NH-tetrazoles under conditions that in most cases do not require heating and often provide higher regioselectivity of alkylation.

Results and Discussion

Tetrazole **1a** and phenyl diazoacetate **2a** were chosen as model substrates to optimize the conditions for the alkylation reaction (Table 1). The test reactions were carried out in DCM and DCE, which are highly inert towards carbenoids generated from diazo reagents. As can be seen from the results presented in Table 1, all catalysts tested, including rhodium carboxylate complexes, copper complexes and triflic acid, successfully decomposed the diazo compound, leading to the formation of N–H insertion products **3a** and **4a**, the yields and ratios of which were evaluated using ^{1}H NMR data. The best yields were observed with rhodium catalysts, which were effective at room temperature (entries 1–4). The reaction in the presence of copper derivatives required a significant increase in temperature and the yields were noticeably lower (entries 5, 6). The use of TfOH as a catalyst (as in the case of CuTC, entry 6) led to the formation of regioisomeric products in almost equal proportions and moderate yields (entry 7). We also tried different TfOH loadings and lower temperatures, but these did not significantly improve the overall reaction yield and did not affect the ratio of regioisomeric alkylation products. Among the rhodium catalysts, the best result, both in terms of yield and regioselectivity, was obtained with $Rh_2(OAc)_4$ (entry 2). And despite the fact that the reaction was slower in this case (full conversion was not

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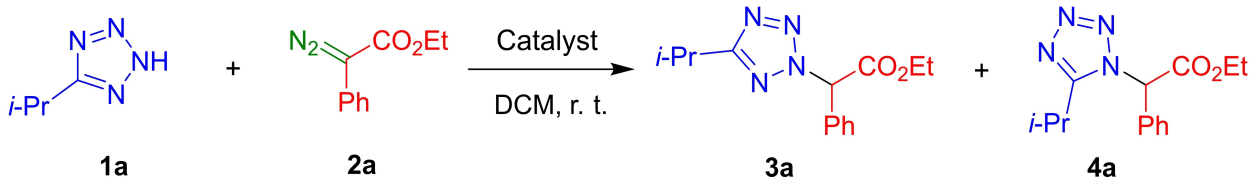
Table 1. Optimization of the N–H insertion reaction conditions.[a,b]



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

Entry	catalyst (mol %)	time (h)	ratio **3a**/**4a**	yield (%) **3a**/**4a**
1	$Rh_2(esp)_2$ (0.1)	1	87:13	63:9
2	$Rh_2(OAc)_4$ (1)	12	97:3	80:2
3	$Rh_2(TFA)_4$ (1)	1	87:13	67:10
4	$Rh_2(OPiv)_4$ (1)	1	86:14	65:10
5[c]	$Cu(acac)_2$ (5)	1	86:14	42:7
6[c]	CuTC (5)	24	56:44	28:22
7	TfOH (20)	1	47:53	25:28

[a] Reactions were run with 0.18 mmol of **1a**, 0.20 mmol of **2a**, and 1.0 mL of DCM. [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 performed in DCE at 100 °C in a sealed vessel.

achieved in 3 hours and the reaction was kept overnight), it was the dirodium tetraacetate, which is also the most available among the Rh(II) carboxylates, that we chose for further studies.

The reaction between tetrazole **1a** and diazo reagent **2a** catalyzed by $Rh_2(OAc)_4$ was carried out on a larger scale (0.45 mmol of **1a** and 0.5 mmol of **2a**), resulting in the isolation of the product **3a** in 88% yield (see Table 1) after flash chromatography of the reaction mixture without any work-up. We also carried out the reaction under TfOH catalysis on a larger scale in order to isolate the second 1-*N*-substituted regioisomer **4a** and to confirm its structure. In this case, both regioisomers were successfully separated by silica gel column chromatography with yields of 28% for **3a** and 30% for **4a** (see Supporting Information).

With both regioisomers in individual form, we turned to the search for reliable criteria to confirm their structure. It is known that for regioisomeric 1-*N*- and 2-*N*-substituted tetrazoles the chemical shifts of the ring carbon atom usually differ significantly and are in the range of 150–155 ppm (for the 1-*N*-isomer) and 160–165 ppm (for the 2-*N*-isomer). This has been shown for some 5-aryl substituted tetrazoles,[22] and often the same trend holds true for other disubstituted derivatives. However, there are examples where the chemical shift of the ring carbon atom signal is outside these intervals and it is difficult to assign the structure unambiguously to a particular isomeric form without having a second regioisomer for comparison.[23] Furthermore, given that fragments introduced into the tetrazole cycle may contain carbon atoms with similar chemical shifts, we would like to have a more reliable criterion that unambiguously indicates the structure of one of the regioisomers. A possible alternative is the detection of the nuclear Overhauser effect (NOE) using two-dimensional NOESY spectra. Indeed, for the 1,5-disubstituted tetrazole **4a**, where the substituents are close together, cross-peaks are observed corresponding to protons through space interactions (Figure 2). And for the 2,5-substituted regioisomer **3a** there are no such cross-peaks in the NOESY spectrum. However, to use this criterion it is necessary to have both regioisomers, which is inconvenient and not always possible. If only the 2-*N*-substituted isomer is available, the absence of a cross-peak in the NOESY spectrum cannot serve as a reliable confirmation of its structure.

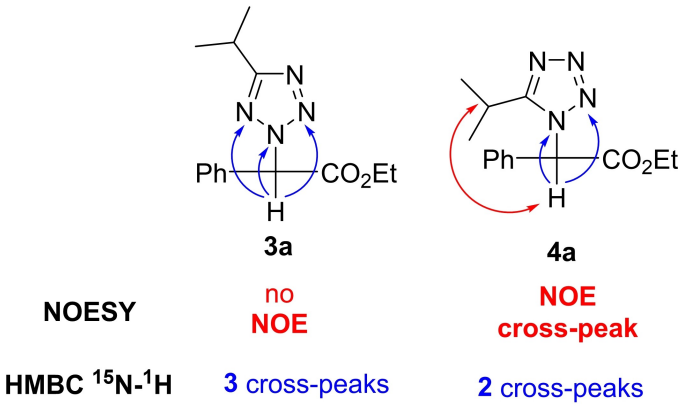


Figure 2. Correlations in 2D NMR spectra for regioisomers **3a** and **4a**.

As a solid NMR criterion that can be relied upon in most cases, we used correlations in the two-dimensional HMBC ^{15}N-^{1}H spectrum,[24] which show the interaction of the proton in the substituent introduced into the tetrazole with two (for 1-*N*-substituted regioisomer) or three (for 2-*N*-substituted regioisomer) nitrogen atoms of the ring, respectively (Figure 2). For all the substituted tetrazoles obtained in this work we have recorded these spectra, which unambiguously confirm their structure. In addition, we have obtained single crystal X-ray diffraction data for some of the products (see Supporting Information).

Having established optimal conditions for the regioselective alkylation of tetrazoles and a reliable method for their structural

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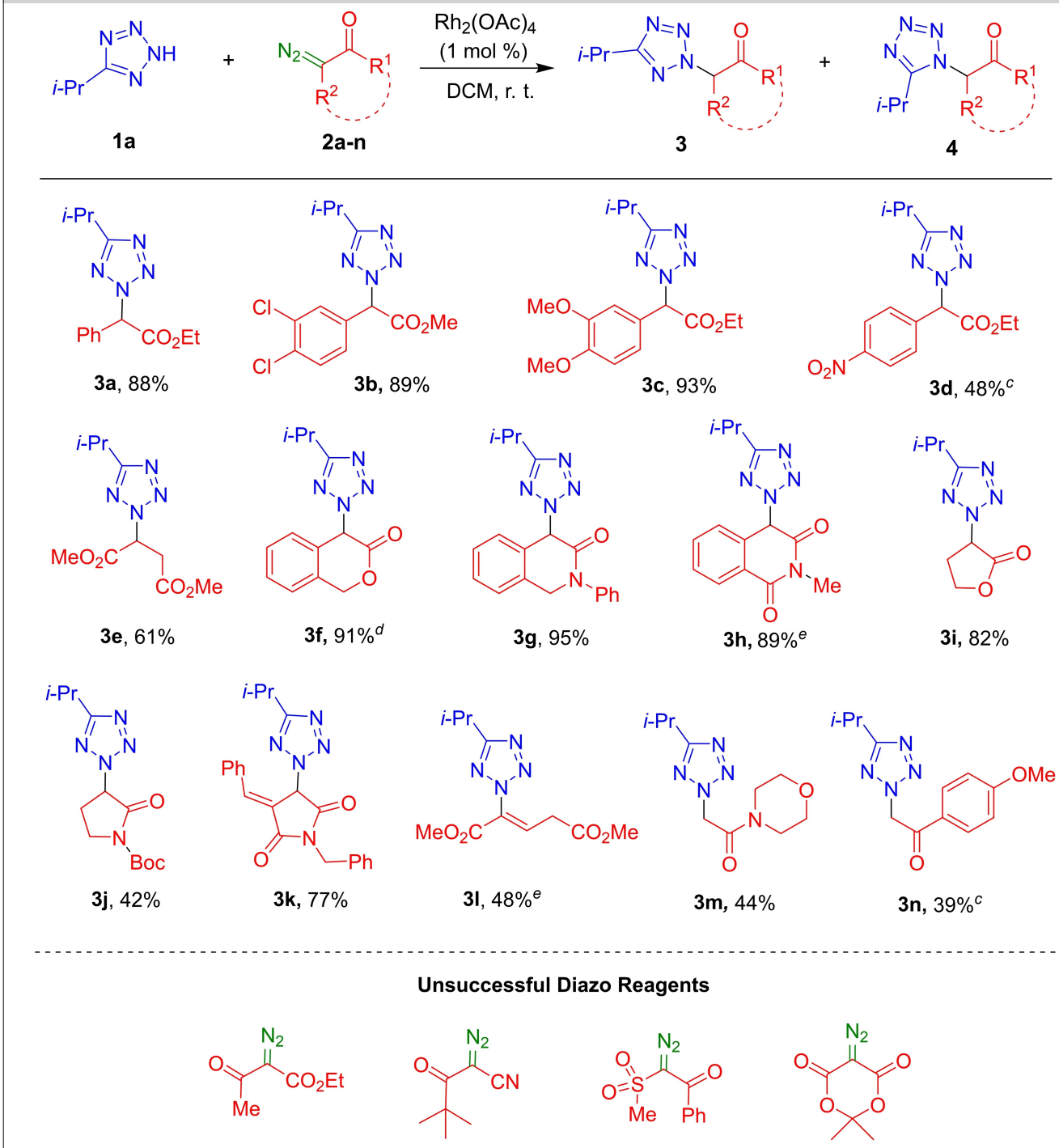
confirmation, we turned to the study of the possibility of modifying the tetrazole 1a as a result of its interaction with structurally diverse diazo reagents (Table 2). With a series of substituted aryldiazoacetates, regioselective N–H insertion reaction products were successfully obtained (**3 b–d**). The reaction with the nitro-substituted diazo derivative **2 d** (the numbering of the diazo reagents corresponds to that given in the Supporting Information) was much slower, and moderate heating was required to accelerate it. In this case the yield of the target compound **3 d** was reduced.

Next, by introducing other diazo reagents into the reaction, we managed to attach to tetrazole **1 a** fragments of succinate

Table 2. Scope of diazo reagents.[a,b]



[a] Reactions were run with 0.45 mmol of **1 a**, 0.5 mmol of diazo reagent **2**, and 2.0 mL of DCM using 1 mol % of $Rh_2(OAc)_4$. [b] Isolated yields. [c] Reaction was performed at 50 °C in a sealed vessel. [d] Single-crystal X-ray analysis data were obtained[26] (see Supporting Information). [e] Reaction was catalyzed with 0.1 mol % of $Rh_2(esp)_2$.

ester (**3e**), various six- and five-membered heterocycles, including isochromanone (**3f**), isoquinolinone (**3g,h**), butyrolactone (**3i**), butyrolactam (**3j**) and succinimide (**3k**). Diazoglutaconic ester (product **3l**), diazoacetamide (product **3m**) and diazoacetophenone (product **3n**) were also reacted. Although the yields in the last three examples were not high, the reaction results were generally more successful. In some cases, with less reactive diazo compounds the reaction proceeded too slowly under the action of $Rh_2(OAc)_4$ and a more active catalyst, $Rh_2(esp)_2$ (for **3h** and **3l**), was used. It should be noted that in all cases (including the examples with average yields) the reaction proceeded with high regioselectivity, the formation of the second regioisomer **4** was not detected or was observed in the spectra of the reaction mixtures only in trace amounts (< 5%).

Separate mention should be made of product **3l**, whose formation involved migration of the double C=C bond in addition to N–H insertion. According to the ^{1}H NMR spectrum, the obtained substance contains small amounts of a minor *E*-configured stereoisomer and a regioisomer with a different arrangement of the double bond. The configuration of the main product was established by comparison of the coupling constants $^3J_{C-H}$ (see Supporting Information) using a selective variant of the method described in the literature.[25]

The low yields of products **3m** and **3n** should not worry us too much, since obviously compounds of this type can be obtained by standard alkylation of tetrazoles under the action of the corresponding readily available halides (α-chloro(bromo)-acetamides and acetophenones). A major limitation of the transformation studied was the impossibility of obtaining products using diazo reagents containing, in addition to the carbonyl group, another electron-withdrawing function (diazo ketoether, ketonitrile, ketosulphone and diazo Meldrum's acid) (Table 2). We attempted to run these reactions under different conditions, varying the catalyst and temperature regime, but were unable to detect the formation of the target compounds. Whilst the diazo Meldrum's acid did not enter the reaction at all, complex multi-component mixtures were obtained for the keto derivatives under conditions to achieve full conversion of the diazo reagent. It cannot be excluded that this result is due on the one hand to the reduced reactivity of such diazo reagents and on the other hand to the insufficient stability of the final products under the harsh reaction conditions used to overcome their inertness.

The next stage of the work was to investigate the influence of the electronic and steric properties of the substituent in the tetrazole on the course of the N–H insertion reaction (Table 3). For this purpose, and to demonstrate the versatility of the method, various 5-alkyl tetrazoles differing in the size of the substituent (R=Me, Et, Adm, Bn) or containing electron-withdrawing groups (R=CH_2Cl and CH_2CO_2Et), as well as 5-aryl substituted tetrazoles and some other substrates, including ethyl tetrazol-5-carboxylate (R=CO_2Et), were introduced into the reaction with the diazo reagent **2a** (as well as other diazo compounds). It should be noted that in many cases the conversion of the diazo reagent at room temperature was too slow or not observed at all, which may be partly due to the reduced solubility of some tetrazoles in DCM. In such cases we used heating (50 °C in DCM or 100 °C in DCE) or a more active catalyst ($Rh_2(esp)_2$) to accelerate the reaction.

In most cases, the reaction proceeded regioselectively, and the target 2-*N*-modified tetrazoles **3** were obtained in good yields (Table 3), while the formation of regioisomer **4** was not detected or observed only in trace (< 5%) amounts. Nevertheless, sometimes we observed the formation of considerable amount of the second regioisomer, which could be isolated (**4w**) or its yield could be estimated from NMR spectra (**4r**). In some cases, namely with tetrazoles containing chloromethyl and ester groups, both regioisomers (**3x/4x** and **3y/4y**) were formed in commensurate amounts and were isolated individually by column chromatography.

Due to the reduced solubility of aryl-substituted tetrazoles in DCM, reactions with them had to be carried out in DCE at 100 °C. In these cases, the use of excess phenyldiazoacetate led to difficulties in the purification of the target compounds from the product of the self-coupling of diazo reagent **2a** – diethyl 2,3-phenylmaleate (a known by-product).[27] Therefore, equimolar amounts of reagents were used in these reactions and the corresponding tetrazole derivatives **3s–v** were isolated in moderate yields of 41–58% as a single regioisomer.

In the reaction with the cyclic vinyl diazocarbonyl reagent – diazo pyranone **2o** – the product of N–H insertion with a migrated double bond (**3z**) was obtained, similar to the previously observed result of the reaction with diazo glutaconic ester (product **3l**). Using another diazo heterocyclic reagent **2p**, glutarimide derivatives **3aa–3ac** containing a tetrazole substituent at the α-position were also obtained. Using the reaction with ethyl tetrazol-5-carboxylate as an example, it can be observed that the N–H insertion with diazo glutarimide is characterized by a higher regioselectivity (see ratios **3ab/4ab** 64%:11% vs **3y/4y** 33%:45%). These modified glutarimides (after removal of the protecting group) can be considered as promising ligands of the Cereblon-based E3 ubiquitin ligase (analogues of so-called immunomodulatory imide drugs, IMiDs)[28] for the design of heterobifunctional molecules known as proteolysis-targeting chimeras (PROTACs)[29] or molecular glues[30] for the targeted protein degradation (TPD).

The regioselectivity of the N–H insertion reaction involving tetrazoles can be determined by many factors, including the steric and electronic properties of the substituent at position 5 of the ring and the ratio of the two tautomeric 1-NH and 2-NH forms of the starting tetrazole. In addition, the direction of attack also depends on the structural characteristics of the diazo reagent used. Because of the variety of factors involved and their mutual influence, it is difficult at this stage to identify clear patterns and to pinpoint the causes that determine a particular reaction outcome. However, it should be noted that the steric factor of the substituent in tetrazole does not seem to play a significant role. As can be seen, for 5-methyltetrazole (with the smallest substituent) only the product **3o** was obtained and the formation of a second regioisomer was not observed, whereas for substrates with larger substituents the 1-*N*-substituted regioisomers **4r** (for R = benzyl) and **4w** (for R = thiophen-2-ylmethyl) were detected or even isolated. There is

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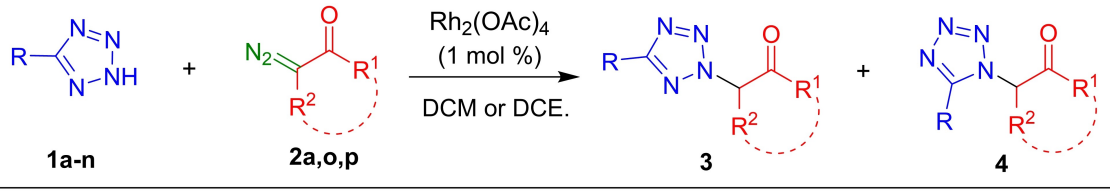
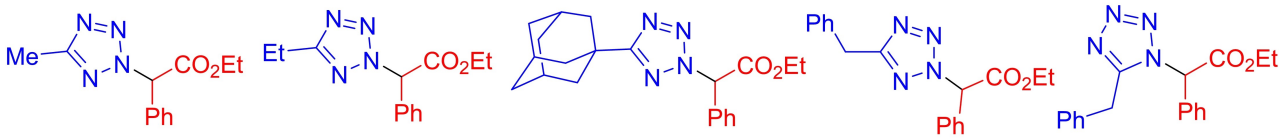
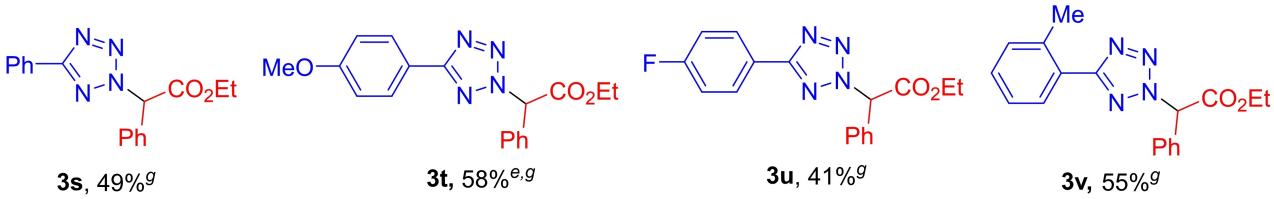
Table 3. Scope of NH-tetrazoles.[a,b]



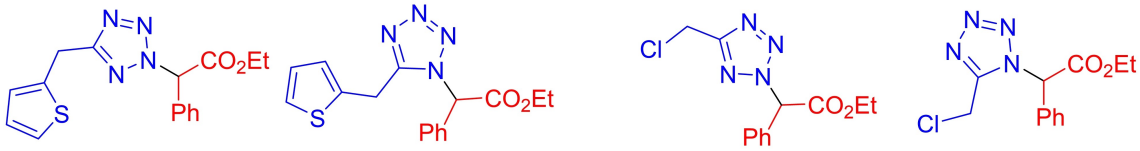
1a-n **2a,o,p** **3** **4**



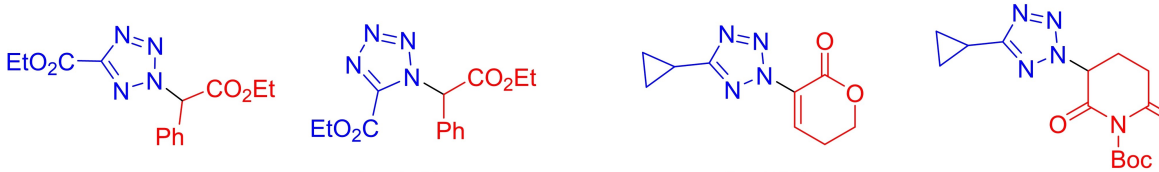
3o, 63%[c] **3p**, 77%[d] **3q**, 52%[e] **3r**, 61%[d] and **4r**, (11%)[f]



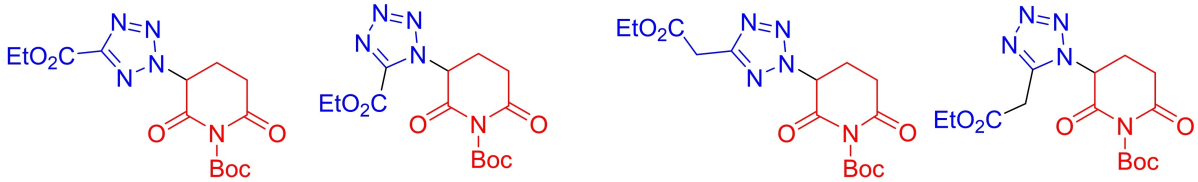
3s, 49%[g] **3t**, 58%[e,g] **3u**, 41%[g] **3v**, 55%[g]



3w, 55%[d] and **4w**, 11% **3x**, 49%[d] and **4x**, 24%



3y, 33% and **4y**, 45% **3z**, 58% **3aa**, 78%



3ab, 64% and **4ab**, (11%)[f] **3ac**, 74% and **4ac**, 8%

[a] Reactions were run with 0.45 mmol of **1a**, 0.5 mmol of diazo reagent **2**, in 2.0 mL of DCM at r. t. using 1 mol % of $Rh_2(OAc)_4$. [b] Isolated yields. [c] Reaction was catalyzed with 0.1 mol % of $Rh_2(esp)_2$. [d] Reaction was performed at 50 °C in a sealed vessel. [e] Single-crystal X-ray analysis data were obtained[26] (see Supporting Information). [f] NMR yield is given in parentheses (internal standard – 2,4-dinitrotoluene). [g] Reaction was performed in DCE at 100 °C in a sealed vessel with 0.45 mmol of **2a**.

also a tendency for the regioselectivity of the reaction to decrease in the presence of a substituent with electron withdrawing properties in the tetrazole (for **1k**, **1l** and **1n**, the numbering of the NH-tetrazoles corresponds to that given in the Supporting Information). It is difficult to say whether this is due more to the shift in the tautomeric equilibrium in NH-tetrazole or to the change in the charge and orbital characteristics of the nitrogen atoms.

Mechanistically, the reaction appears to be similar to other Rh(II)-catalyzed X–H insertions involving diazocarbonyl compounds (Scheme 1). Perhaps the only specificity is that the intermediate rhodium carbenoid attacks the tetrazole ring (shown in the example of the 1*H*-tautomer) on one of the more

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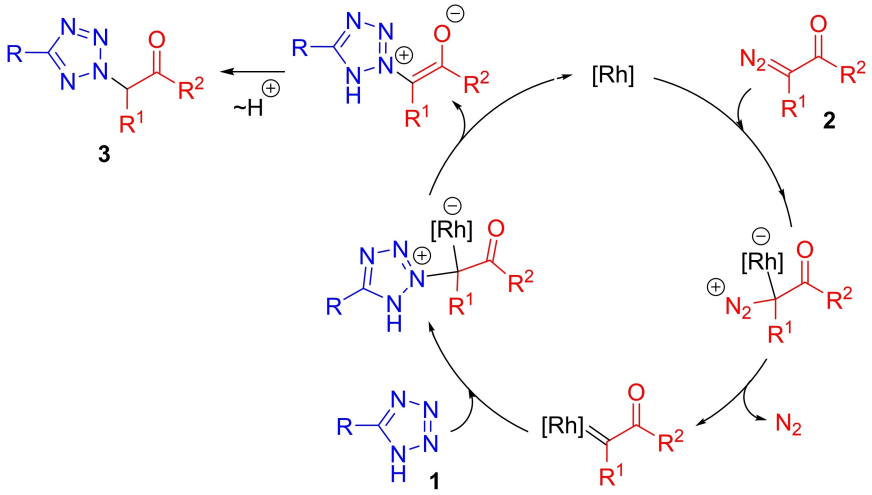

Scheme 1. Plausible mechanism for Rh(II)-catalyzed N–H insertion into tetrazoles.

nucleophilic pyridine-type nitrogens (not NH), resulting (after loss of the catalyst) in the formation of a tetrazolium ylide which undergoes a rapid prototropic transition to the final form.

In studying the reaction of tetrazole **1l** (R=CO_2Et) it was found that N–H insertion can occur without the involvement of a catalyst. Interestingly, the amount of regioisomer **4y** formed by attacking the 1-N atom of the tetrazole increases significantly in the catalyst-free process. The corresponding products **3y** and **4y** were isolated in 18% and 60% yield respectively. Apparently, the ability of the reaction to proceed without catalysis in this case is due to the increased NH-acidity of tetrazole **1l**, which contains a strong electron withdrawing substituent. This result is consistent with our previously observed effect of increasing the proportion of regioisomer 4 under acid catalysis of the reaction (Table 1, entry 7). This effect and the possibility of its application to the selective preparation of 1,5-substituted tetrazole derivatives will be investigated by us in a subsequent work.

Conclusions

In summary, we have presented a method for the *N*-modification of NH-tetrazoles by N–H insertion reaction using diazocarbonyl compounds. The method allows a wide range of *N*-substituted tetrazole derivatives to be obtained by incorporating structurally diverse fragments (including various heterocycles) into the molecule under mild conditions without the use of bases. The versatility of the approach is demonstrated by the use of a wide variety of diazo reagents as well as various 5-substituted tetrazole substrates. In most cases, the reaction proceeds in good to high yields and is characterized by high regioselectivity, leading predominantly to 2,5-disubstituted tetrazole products, the structure of which is reliably confirmed by NMR experiments and X-ray analysis for selected structures. Compared to the previously published method using aluminium triflate, our work offers a significantly wider range of diazo compounds suitable for *N*-modification of tetrazoles under conditions that in most cases do not require heating and often provide higher regioselectivity of alkylation. The reaction involving vinyl diazocarbonyl compounds leads to *N*-vinylation products formed by sequential N–H insertion and migration of the double C=C bond. It is shown that catalysis of the reaction with acid or the use of tetrazole with increased NH-acidity leads to an increase in the proportion of the minor regioisomer and can be used to obtain both regioisomers or predominantly 1-*N*-substituted derivative.

Supporting Information Summary

See the Supporting Information for full experimental information, X-ray crystallographic data, synthetic procedures, analytical data and NMR spectra for the reported compounds. Additional references cited within the Supporting Information.[31–46]

Funding

This research was supported by the Russian Science Foundation (project grant 22-13-00005).

Acknowledgements

We thank the Research Center for Magnetic Resonance, the Center for Chemical Analysis and Materials Research, and the Center for X-ray Diffraction Methods of Saint Petersburg State University Research Park for obtaining the analytical data.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Tetrazoles · ***N***-alkylation · Diazocarbonyl compounds · Rh(II)-catalysis · N–H insertion reaction

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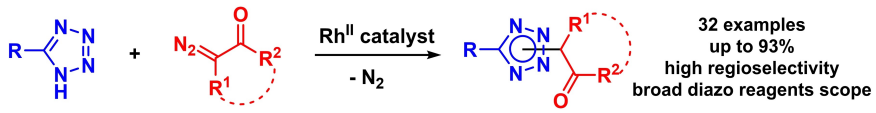
Manuscript received: October 10, 2024
Revised manuscript received: November 11, 2024
Accepted manuscript online: November 20, 2024
Version of record online: ■■, ■■

RESEARCH ARTICLE



A convenient method for the *N*-modification of NH-tetrazoles by the Rh(II)-catalyzed insertion reaction of diazocarbonyl compounds into the N-H bond has been proposed. A wide scope of structurally diverse diazo reagents as well as tetrazoles with different substituents in the fifth position have been used to prepare disubstituted tetrazole derivatives in good and high yields and with high regioselectivity.

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