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Nucleophile-Induced Rearrangement of 2*H*-Azirine-2-carbonyl Azides to 2-(1*H*-Tetrazol-1-yl)acetic Acid Derivatives

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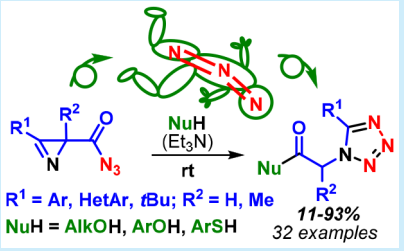
ABSTRACT: 2*H*-Azirine-2-carbonyl azides undergo a rearrangement into derivatives of 2-(1*H*-tetrazol-1-yl)acetic acid when interacting with O- and S-nucleophiles at room temperature. The reaction is catalyzed by tertiary amines or hydrazoic acid. The reaction with primary alcohols and phenols gives alkyl/aryl 2-(1*H*-tetrazol-1-yl)acetates. Thiophenols react with 2*H*-azirine-2-carbonyl azides to afford *S*-aryl 2-(1*H*-tetrazol-1-yl)ethanethioates. The mechanism of the nucleophile-induced rearrangement of 2*H*-azirine-2-carbonyl azides is discussed on the basis of DFT calculations as well as kinetic and ^{15}N labeling experiments.

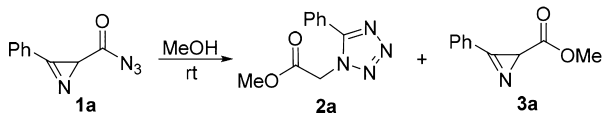


Rearrangements of highly strained 2*H*-azirines allow the preparation of a wide range of heterocycles.[1] Thus, various pyridines were prepared by a gold-catalyzed rearrangement of propargyl-substituted 2*H*-azirines,[2] and pyrroles were synthesized via an iron-catalyzed rearrangement of vinyl-substituted isoxazoles, proceeding via intermediate formation of the corresponding azirines.[3] Similarly, indoles,[1a,4] pyrazoles,[5] and oxazoles[6] were synthesized. Rearrangements of 2*H*-azirines with any substituents leading to heterocycles containing more than two nitrogen atoms are, to the best of our knowledge, still unknown.[1] Recently the synthesis of 2*H*-azirine-2-carbonyl azides was developed and used for the preparation of polyheterocycles.[7] It was found that when azide **1a** was heated in MeOH or *tert*-BuOH to obtain the corresponding azirin-2-ylcarbamate via Curtius rearrangement, it led to extensive tarring. But recently by serendipity we found that 3-phenyl-2*H*-azirine-2-carbonyl azide **1a** in MeOH at room temperature undergoes a quite unusual reaction leading to the formation of methyl 2-(5-phenyl-1*H*-tetrazol-1-yl)acetate **2a** (59%) as the main product and azirine **3a** (7%) as byproduct. Taking into account that tetrazoles found broad applications in numerous fields such as medicine, biochemistry, pharmacology, and industry,[8] it was decided to study this reaction in detail. The structure of the unexpected tetrazole **2a** was determined from its ^{1}H, ^{13}C, ^{15}N, and $^{1}H-^{15}N$ HMBC NMR spectra, which excellently corresponds to literature data for ethyl 2-(5-phenyl-1*H*-tetrazol-1-yl)acetate.[9] The formation of 1,5-disubstituted tetrazole **2a** implied a significant rearrangement of the starting azirine skeleton.

A rearrangement is a key part of processes leading to 1,5-disubstituted tetrazoles in the Schmidt reaction of ketones with azides[10] and diphenyl phosphorazidate-mediated Beckmann rearrangement of ketoximes.[11] The nitrogen atoms of the forming tetrazole ring in these reactions come from the external azide derivative.

There are few examples of the formation of nonfused tetrazoles in which all nitrogen atoms for the construction of the tetrazole ring are present in the starting material. Thus, L'abbé et al. have discovered the thermal isomerization of 4-alkoxycarbonyl-5-azide-1,2,3-triazoles into 5-(diazomethyl)-tetrazoles.[12] The formation of 1,2,3-triazolo-fused heterocycles from azido-substituted pyridine, pyrimidine, triazine, and azole derivatives, the so-called azide-tetrazole ring−chain tautomerism, is much more known.[10a,13] In these reactions, the azido-functional group is bonded to a nitrogen-substituted carbon; i.e., the sequence of N−N−N−C−N atoms required to create a tetrazole skeleton is already present in the starting materials. This is not the case in the rearrangement shown in Scheme 1. Therefore, in order to understand the mechanism of discovered rearrangement, we first decided to determine where the azirine nitrogen is in product **2** by conducting an experiment with labeled azirine **1b** (Scheme 2). Based on ^{15}N NMR data for ethyl 2-(5-phenyl-1*H*-tetrazol-1-yl)acetate[9] and

Scheme 1. Transformations of Azirine 1a



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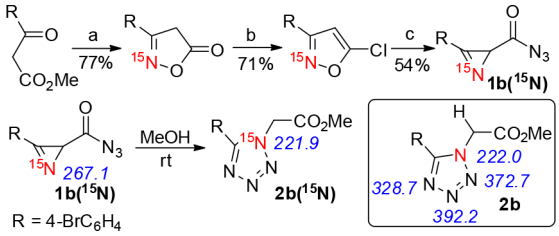
Scheme 2. Synthesis and Rearrangement of the Labelled Azirine 1a[a]



[a]Reagents: (a) $HO^{15}NH_2$·HCl; (b) $POCl_3$, NEt_3; (c) (1) $FeCl_2$, (2) NaN_3.

1,5-diphenyl-1*H*-tetrazole,[14] the ^{15}N NMR signals of **2b** were assigned as follows: 222.0 (N1), 328.7 (N4), 372.7 (N2), and 392.2 ppm (N3). In the ^{15}N NMR spectrum of **2b(15N)**, the most intensive peak is at 221.9 ppm, so we can conclude that azirine nitrogen of **1** appears as the N1 in the tetrazole **2b**. The structure of tetrazole **2b** was also confirmed by single-crystal X-ray diffraction analysis.

To obtain information on the rates of consumption of the starting azidocarbonylazirine and the formation of the target tetrazole, as well as a possible intermediate and/or byproducts (one of which is azirine **3**), kinetic ^{19}F NMR experiments were carried out using azirine **1c** as starting material and 4-(trifluoromethyl)benzonitrile, which is inert under the reaction conditions, as an internal standard (Figure 1). According to the

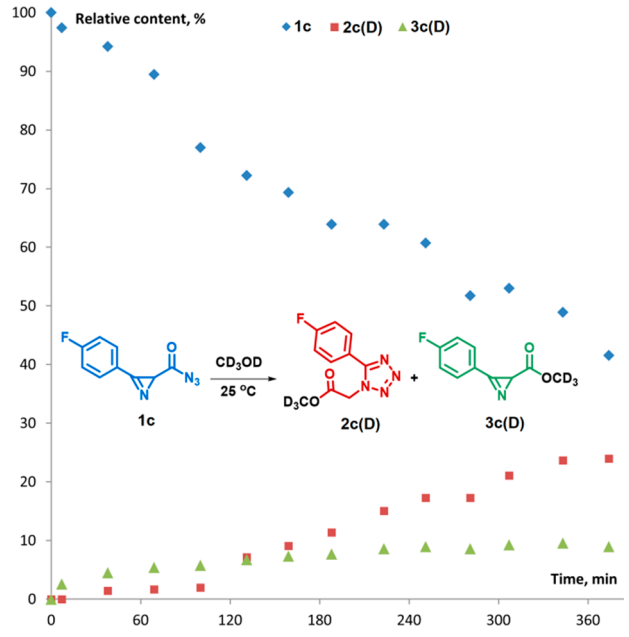


Figure 1. Time dependence of the relative content of **1c**, **2c(D)**, and **3c(D)** in the reaction mixture based on the integral intensities of ^{19}F NMR signals normalized to the internal standard.

data obtained, the concentration of methoxycarbonylazirine **3c(D)** in the reaction mixture increases faster during the first 2 h than the concentration of tetrazole **2c(D)**, and then the concentration of tetrazole **2c(D)** continues to increase, while the concentration of methoxycarbonylazirine **3c(D)** remains almost constant. This may mean that either azirine **3c(D)** is an intermediate product on the way to tetrazole **2c(D)** or, when it is formed from azidocarbonylazirine **1**, N_3^-/HN_3 is simultaneously released, which is necessary to trigger the rearrangement. To gain insight into the mechanism of the rearrangement, the quantum chemical calculations of the transformation of azirine **1a** to tetrazole **2a** were performed at the B3LYP-D3/6-311+G(d,p) level of theory with the SMD model for methanol (Figure 2; for details of the calculations, see the Supporting Information).

According to the calculations, methanol cannot extrude HN_3 directly from azirine **1a** to give azirine **3a**, while MeO^- reacts without an energy barrier with azirine **1a** to give azirine **3a** and the azide anion. The formation of MeO^- can be the result of an equilibrium reaction between methanol and a base, and since the azirine is initially the only base in the reaction mixture and it is weak, the concentration of the methoxide must be very low. Neither azirine **1a** nor azirine **3a** is capable of adding a nucleophilic azide anion to the C=N double bond, while the corresponding protonated azirines easily react with the azide anion. Thus, complexes ***A*** and ***B*** of azirines **1a** and **3a** with HN_3 give azidoazirines ***C*** and ***D*** through the energy barriers, which are surmountable at rt. The route from diazidoaziridine ***C*** to tetrazole **2a** (Figure 2, blue route) involves conformational transformations ***C*** → ***E*** → ***F***, the aziridine ring opening in ***F*** with formation of the stabilized W-azomethine ylide ***G***, followed by its isomerization to *S*-azomethine ylide ***H*** and extrusion of HN_3 from the latter to give ketene ***I***. The reaction of ketene ***I*** with MeOH affords azidoimine ***J*** which transforms to the conformation ***K***, suitable for the cyclization of azidoimine ***K*** to tetrazole **2a**. According to the calculations, all the mentioned transformations proceed through energy barriers surmountable at rt. Similarly, azidoaziridine ***D*** can give tetrazole **2a** via the transformations ***D*** → ***L*** → ***M*** → ***N*** → ***O*** → ***I*** → ***J*** → ***K*** (Figure 2, yellow route), but this route passes through **TS12** with a higher relative Gibbs free energy (24.4 kcal/mol) than **TS5** (19.7 kcal/mol), so these routes do not compete as long as azirine **1a** is present in the reaction mixture.

According to the presented mechanism (Figure 2), acid–base relationships in the reaction mixture should have an influence on the rearrangement rate. To check this, an additional experiment with fluorinated azirine **1c** and CD_3OD in the presence of 20 mol % Et_3N, using ^{19}F NMR, was performed (Figure 3).

According to the results obtained, the addition of Et_3N significantly accelerates the reaction. Thus, the concentration of tetrazole **2c** in the presence of Et_3N reaches a maximum already in 3 h (Figure 2), whereas, without a base, it reaches a maximum in 6 h (Figure 3). The effect can be attributed to an increase in the concentration of MeO^-, which promotes the release of N_3^-. Several other bases (DMAP, TMEDA) also accelerate the reaction, in contrast to pyridine, which has no effect. The base and their amount have practically no influence on the yield of the target tetrazole **2a**, but the amount of the byproduct, azirine **3a**, is affected (see Table S1 in the Supporting Information).

According to the presented mechanism (Figure 2), the addition of HN_3 should catalyze the rearrangement. To check this, an additional experiment with fluorinated azirine **1c** and CD_3OD in the presence of 20 mol % N_3H, using ^{19}F NMR, was performed (Figure 4). Indeed, in full agreement with the proposed mechanism the N_3H additive catalyzes the reaction. Moreover, this additive increases the tetrazole yield and makes the spectral overall yield tetrazole **2c(D)** + **3c(D)** practically quantitative, probably due to the fact that the additive

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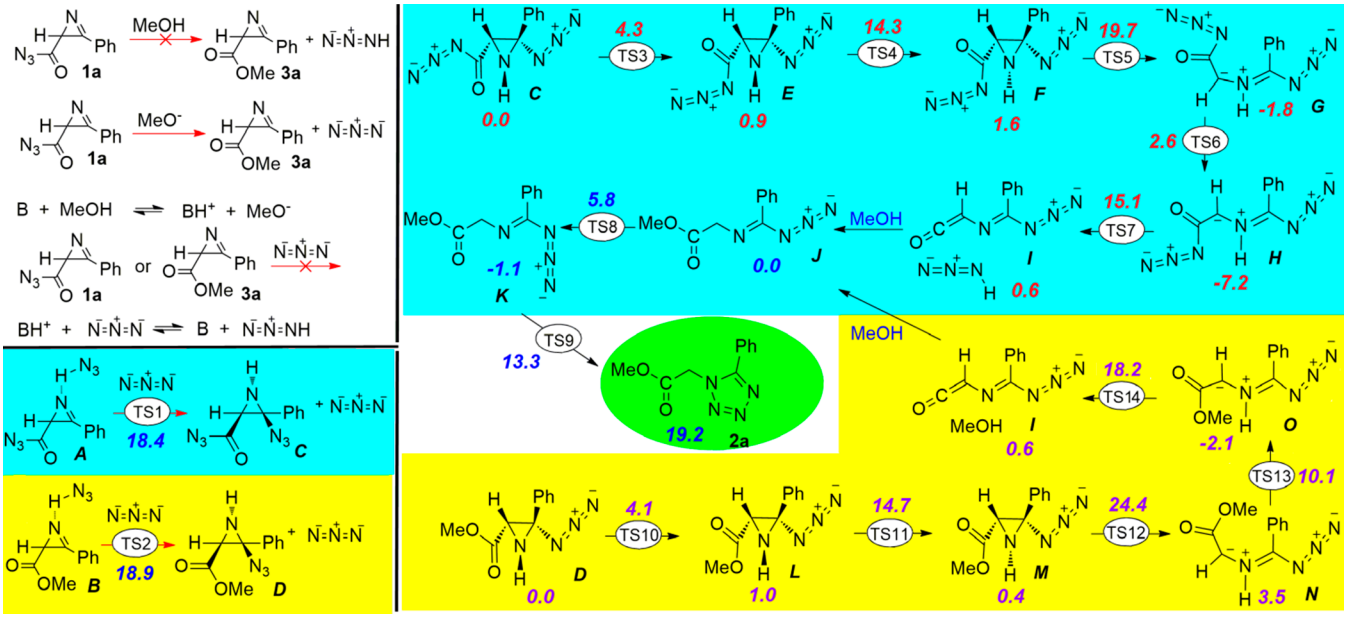

Figure 2. Plausible mechanism of the rearrangement based on the DFT calculations (relative Gibbs free energies for the reaction energy profiles in kcal/mol, 298 K, DFT B3LYP-D3/6-311+G(d,p) level with SMD model for methanol).

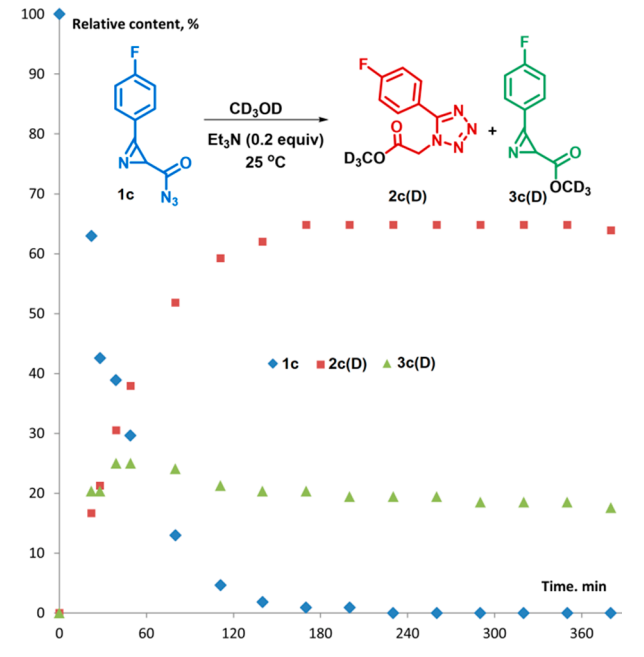

Figure 3. Rearrangement of azirine **1c** in CD_3OD in the presence of 20 mol % Et_3N.

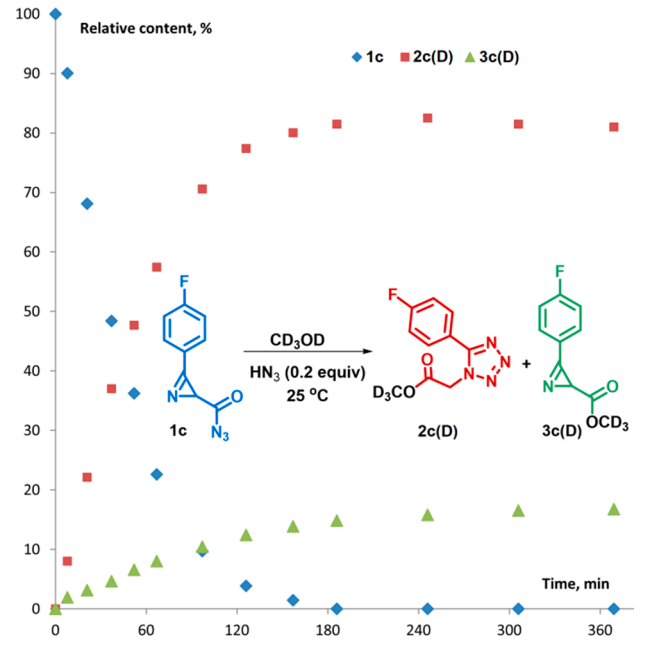

Figure 4. Rearrangement of azirine **1c** in CD_3OD in the presence of 20 mol % N_3H.

compensates for the losses of N_3^-/HN_3, formed from internal sources, due to side processes.

The methanol-induced isomerization was further carried out with azidoazirines **1a**–**l** to obtain the tetrazoles **2a**–**l** (Scheme 3). To avoid working with explosive N_3H, an additive of Et_3N was used as a promoter where necessary.

In the reactions of azirines **1f**, **g**, **i**, incomplete conversions and low yields were observed, and neither an increase in the reaction time nor the addition of a base improved the yields. *tert*-Butyl-substituted azirine **1l** did not react with methanol in the absence of a base; nevertheless, tetrazole **2l** was obtained in the presence of Et_3N (10 mol %). The use of various alcohols in the reaction of azirine **1a** allows the preparation of a series of esters of 2-(5-phenyl-1*H*-tetrazol-1-yl)acetic acid **4a**–**c**. The reactions proceeded at an acceptable rate only in the presence of Et_3N (Scheme 4). The reactions with EtOH, CF_3CH_2OH were carried out in the corresponding alcohol as a solvent, and with BnOH, in acetonitrile. Bulkier alcohols such as *i*PrOH and *t*BuOH did not react with azirine **1a**.

Phenols were found to be even more suitable reagents for realizing the rearrangement, giving in the presence of Et_3N (10 mol %) high yields of the previously unknown aryl esters of 2-(1*H*-tetrazol-1-yl)acetic acid, **5a**–**l** (Scheme 5). Strong electron-withdrawing substituent in the phenol such as CO_2Et reduces the yields of product (**5j**). Phenols containing

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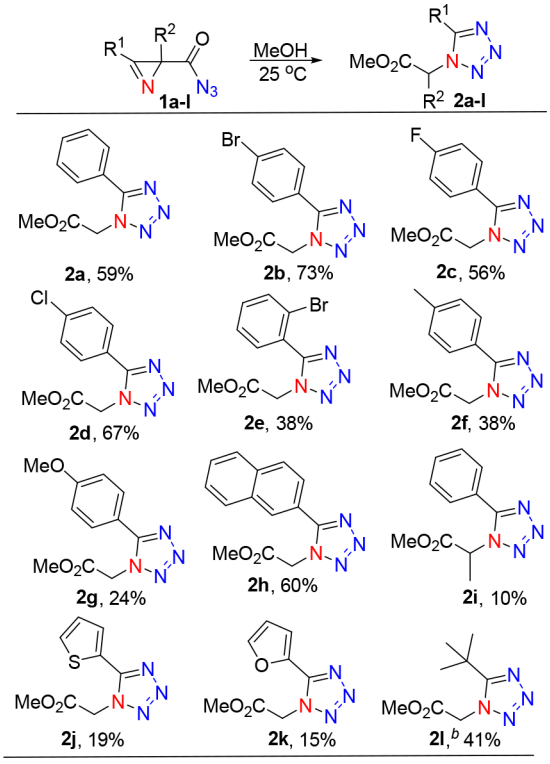
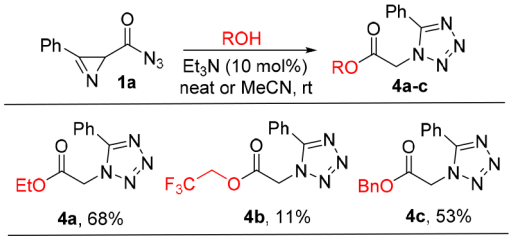
Scheme 3. Synthesis of Tetrazoles 2a–l[a]



[a]Isolated yield. Reaction conditions: **1** (0.25 mmol), MeOH (6 mL), rt, 1–2 d. [b]In the presence of Et_3N (10 mol %).

Scheme 4. Synthesis of Tetrazoles 4a–c[a]



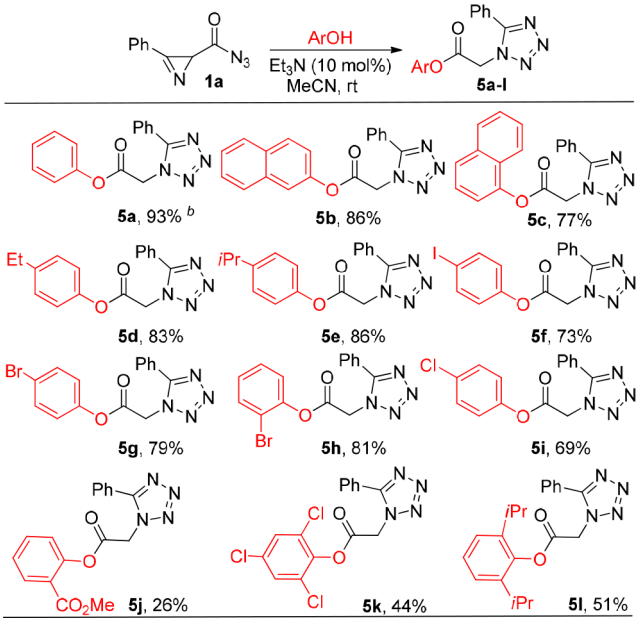
[a]Isolated yield. Reaction conditions: **1a** (0.30 mmol), ROH (6 mL), Et_3N (0.03 mmol), (for **4a,b**); **1a** (0.27 mmol), BnOH (0.36 mol), Et_3N (0.027 mmol), MeCN (4 mL) (for **4c**); rt, 2 d.

ortho and even di-*ortho* substituents react with azirine **1a** (**5h, j, k, l**).

We also succeeded in carrying out this new rearrangement in the presence of thiophenols as nucleophiles. As a result of the reaction, the previously unknown *S*-aryl 2-(5-phenyl-1*H*-tetrazol-1-yl)ethanethioates **6a–e** were obtained in moderate yields (Scheme 6).

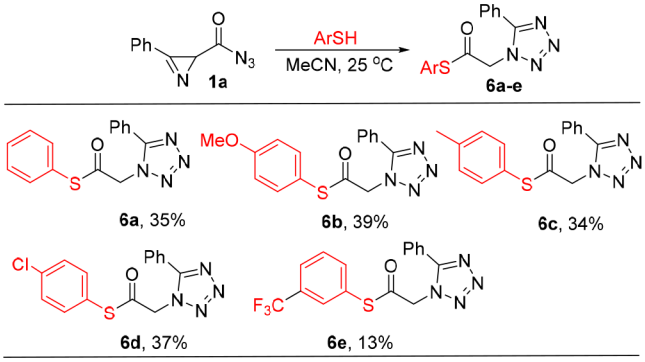
In conclusion, 2*H*-azirine-2-carbonyl azides undergo an unusual rearrangement into derivatives of 2-(1*H*-tetrazol-1-yl)acetic acid when interacting with O- and S-nucleophiles at room temperature. It was found that the rearrangement is catalyzed by tertiary amines or hydrazoic acid. The reaction of 2*H*-azirine-2-carbonyl azides with methanol can proceed without basic catalysis to give methyl 2-(1*H*-tetrazol-1-yl)acetates, whereas reaction with EtOH, CF_3CH_2OH, and BnOH proceeds at an acceptable rate only in the presence of Et_3N. Phenols react under similar conditions to give generally good yields of the corresponding aryl esters of 2-(1*H*-tetrazol-1-yl)acetic acid. Thiophenols react with 2*H*-azirine-2-carbonyl azides to give previously unknown *S*-aryl esters of 2-(5-phenyl-1*H*-tetrazol-1-yl)thioacetic acid in moderate yield. A plausible mechanism of the nucleophile-induced rearrangement of 2*H*-azirine-2-carbonyl azides was proposed on the basis of DFT calculations and kinetic experiments.

Scheme 5. Synthesis of Tetrazoles 5a–l[a]



[a]Isolated yield. Reaction conditions: **1a** (0.27 mmol), ArOH (0.36 mol), Et_3N (0.027 mmol), MeCN (4 mL), rt, 2 d. [b]The gram-scale synthesis: 1.022 g (73%).

Scheme 6. Synthesis of Tetrazoles 6a–e[a]



[a]Isolated yield. Reaction conditions: **1a** (0.27 mmol), ArSH (0.36 mol), MeCN (4 mL), rt, 2 d.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02157.

Experimental procedures; characterization data; calculation details; X-ray data of compound **2b**; ^1H, ^{13}C and ^{19}F NMR spectra (PDF)

Accession Codes

CCDC 2091489 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge

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via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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