Generation of Sulfonylated Tetrazoles through an Iron-Catalyzed Multicomponent Reaction Involving Sulfur Dioxide

HIGHLIGHTS

High-value tetrazole motifs were synthesized via a five-component reaction

Fixing sulfur dioxide into tetrazole molecules under mild conditions

Low-cost iron catalyst initiated the transformation

Excellent selectivity with the formation of multiple new chemical bonds

- *mild conditions*
- *low-cost catalyst*
- *excellent selectivity*
- *radical initiated process*
- *late-stage transformation and drug modification*
- *C-C bond cleavage of both alkynes and cycloketone oxime esters*
Generation of Sulfonylated Tetrazoles through an Iron-Catalyzed Multicomponent Reaction Involving Sulfur Dioxide

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SUMMARY
As a privileged motif, tetrazoles can be widely found in pharmaceuticals and materials science. Herein, a five-component reaction of cycloketone oxime esters, alkynes, DABCO\((\text{SO}_2)_2\), and two molecules of trimethylsilyl azide under iron catalysis is developed, giving rise to a range of cyano-containing sulfonylated tetrazoles in moderate to good yields. This multicomponent reaction exhibits excellent selectivity and enables the formation of multiple new chemical bonds in one pot. A possible mechanism involving azidosulfenylation of alkynes, C-C bond cleavage of both cycloketone oxime esters and alkynes, and \([3 + 2]\) cycloaddition of trimethylsilyl azide and the nitrilium cation intermediate is proposed. Additionally, the potential of terminal alkynes acting as powerful synthons for the synthesis of tetrazoles in a radical initiated process is demonstrated for the first time.

INTRODUCTION
Since first synthesized and reported by J. A. Bladin in 1885, the unnatural tetrazoles have become prevalent motifs in pharmaceuticals, biochemistry, and materials science due to their unique characteristic structure and biological activities (Benson, 1947; Fischer et al., 2015; Wei et al., 2015). For instance, tetrazoles have emerged as ideal biosostere of carboxylic acid and cis-amide units because of their more positive pharmacokinetic properties (Juby et al., 1968; Kubo et al., 1993; Peters et al., 2001). Consequently, devising efficient synthetic strategies of various tetrazoles has attracted much attention in organic synthesis. Traditionally, there are two mainstream reaction types for the construction of these valuable compounds: (1) cycloaddition of azides with activated nitriles and (2) cycloaddition of azides with the nitrilium cation intermediates generated in situ from isonitriles, amines, and carbonyl compounds via Ugi multicomponent reaction (Neochoritis et al., 2019). Moreover, several innovative synthetic methods for tetrazoles have been reported recently (Chen et al., 2011; Gaydou and Echavarren, 2013; Hu et al., 2015; Li et al., 2018; Nimnuai et al., 2019; Qin et al., 2016; Wu et al., 2017; Rokade et al., 2014; Ye et al., 2018). Remarkably, Echavarren’s group (Gaydou and Echavarren, 2013) demonstrated that tetrazoles could be prepared from readily available alkynes by C-C single bond cleavage in the presence of Au(I) catalyst (Scheme 1A). Subsequently, Jiao and Shi’s groups (Qin et al., 2016) reported that by using Au(I)/Ag(I) as catalysts and TFOH as an additive, amino tetrazoles were obtained from alkynes through both C-C single bond cleavage and C≡C triple bond cleavage (Scheme 1B). To the best of our knowledge, only these two examples demonstrate that alkynes, serving as versatile and easily available building blocks, are powerful synthons for the formation of valuable tetrazole compounds. Mechanistically, we noticed that alkenyl azides generated by nucleophilic attack onto the alkynes were the key intermediates in these transformations, which could go through protonation and rearrangement to provide nitrilium cation intermediates for further transformations, delivering the final tetrazole motifs. Despite these achievements, generation of tetrazoles with novelty, diversity, and complexity under green and mild conditions is still highly desirable, especially in the field of drug discovery.

Sulfones are subjects of great interest in the area of pharmaceuticals and agrochemicals (Drews, 2000; Feng et al., 2016; Patai et al., 1988). In recent years, sulfonylation reaction via a radical process with sulfur dioxide surrogates, DABCO-(SO₂)₂, and inorganic sulfites, has proven to be a promising approach for the synthesis of diverse sulfone-containing molecules (Bisseret and Blanchard, 2013;
Recently, our group described a copper-catalyzed four-component reaction of terminal alkynes, aryldiazonium tetrafluoroborates, DABCO(SO$_2$)$_2$, and potassium halide, giving rise to a range of $\beta$-halo alkenylsulfones (Xiang et al., 2017). Inspired by this work and recent advances in the reactions of alkynes with trimethylsilyl azide via a radical process (Liu et al., 2019b; Wang et al., 2015; Wu et al., 2019; Xiong et al., 2019; Ning et al., 2017), we conceived that the sulfone-containing alkenyl azide intermediates might be accessed through the azidosulfonylation of alkynes with the insertion of sulfur dioxide via a radical process. Driven by the importance of tetrazole chemistry and our continuous interest in the insertion of sulfur dioxide, we envisioned that the incorporation of sulfonyl unit into tetrazoles for the construction of valuable sulfonylated tetrazoles might be beneficial for various biological evaluations. Very recently, we reported that the cyanoalkyl radicals generated in situ from cycloketone oxime esters (Chen et al., 2019; Dauncey et al., 2018; Deng et al., 2020; Liu et al., 2019a; Wang et al., 2019; Xing et al., 2019; Yin and Wang, 2019; Yin et al., 2018; Yu et al., 2018a, 2018b; Zhang et al., 2019a, 2019b, 2020; Zhao et al., 2018, 2020) through a single electron transfer (SET) reduction with the assistance of copper catalyst or photocatalyst could react with sulfur dioxide to provide sulfonyl radicals for sulfonylation process (Zhang et al., 2019b, 2020). Herein, we report an iron-catalyzed multicomponent reaction of cycloketone oxime esters, alkynes, DABCO(SO$_2$)$_2$, and trimethylsilyl azide, affording a range of sulfonylated tetrazoles in moderate to good yields (Scheme 1C). Cycloketone oxime esters are employed as the precursors to provide the cyanoalkyl radicals through a SET reduction in this sulfonylation process. This multicomponent reaction exhibits excellent selectivity and enables the formation of multiple new chemical bonds in one pot. A possible mechanism involving azidosulfonylation of alkynes, C-C bond cleavage of both cycloketone oxime esters and alkynes, and [3 + 2] cycloaddition of trimethylsilyl

Scheme 1. Synthesis of Tetrazoles from Alkynes and TMSN$_3$

(A) Gold-catalyzed synthesis of tetrazoles from alkynes. (B) Gold/Silver-catalyzed synthesis of amino tetrazoles from alkynes. (C) Iron-catalyzed synthesis of sulfonylated tetrazoles from alkynes.
azide and the nitrilium cation intermediates is proposed. Additionally, the potential of terminal alkynes acting as powerful synthons for the synthesis of tetrazoles in a radical initiated process is demonstrated for the first time.

RESULTS AND DISCUSSION
Optimization of Reaction Conditions
We commenced this multicomponent reaction of O-(4-(trifluoromethyl)benzoyl) oxime 1a, 1-ethynyl-4-methoxybenzene 2a, DABCO-(SO2)2, and trimethylsilyl azide as the model (see Table S1). At the outset, several metal catalysts including Cu(OAc)2, Co(OAc)2, and Fe(OAc)2 were introduced in this transformation to promote the single-electron redox process at 60°C in acetonitrile (Table S1, entries 1–3). Only a trace amount of product was detected when the reaction was treated with copper(II) acetate (Table S1, entry 1). To our delight, the desired sulfonylated tetrazole 3aa was generated in 15% yield in the presence of Co(OAc)2 (Table S1, entry 2). Further exploration revealed that Fe(OAc)2 was a more efficient catalyst, giving rise to the target tetrazole 3aa in 54% yield (Table S1, entry 3).

Substrates Scope with Alkynes and Cycloketone Oxime Esters
After establishing the aforementioned optimized conditions, the generality of substrate scope in this multicomponent reaction was explored (Scheme 2). At the beginning, a range of alkynes 2 was evaluated in the reaction of O-(4-(trifluoromethyl)benzoyl) oxime 1a, DABCO-(SO2)2, and trimethylsilyl azide. All reactions worked well, and various sulfonylated tetrazoles were afforded in moderate to good yields. Various substituents on aryalkynes including alkyl, alkoxy, halo, ester, and N,N-dimethyl were suitable in this transformation. Meanwhile, the structure of compound 3ah was confirmed by X-ray diffraction analysis. Notably, the reaction of 3-ethynylthiophene proceeded smoothly as well leading to the desired product 3at in 53% yield. The expected tetrazole 3as was provided in 51% yield when enyne 2s was used as the substrate. Further extension was made by using 4-methylumbelliferone derivative, endofoliculina derivative, and erlotinib as the starting material, affording the corresponding tetrazole-modified compounds (3au-3aw) in moderate yields, which demonstrated the potential of this methodology for the late-stage modification of more complex molecules. However, the desired product could not be detected when aliphatic alkynes and internal alkynes such as pent-4-yn-1-ylbenzene, ethynylcyclopentane, and prop-1-yn-1-ylbenzene were used in the reaction. Subsequently, the scope of cycloketone oxime esters 1 was examined in the reaction of 1-ethynyl-4-methoxybenzene 2a, DABCO-(SO2)2, and trimethylsilyl azide. As expected, various substituents attached on the quaternary ring of cycloketone oxime esters did not influence the reaction efficiency. For instance, reactions of mono-substituted cycloketone oxime esters with ether, ester, and amide groups at the 3-position worked well to furnish the desired products 3ga-3ia in 59%-68% yields. With allyl or benzyl groups at the 2-position, the imine radicals generated from oxime esters underwent selective C=C bond cleavage to provide the more stable secondary alkyl radicals, thus resulting in the products 3ja and 3ka in 50% and 64% yields, respectively. Additionally, reaction of oxetan-3-one oxime 1m gave rise to the corresponding compound 3ma in 40% yield. In our attempts using five- or six-membered ring substrates, no desired product was observed and the alkyne was recovered.

To evaluate this multicomponent approach on a large scale, 3 mmol 1-ethynyl-4-methoxybenzene 2a (1.0 equiv) was used to perform the model reaction, giving rise to the product 3aa in 58% yield (Scheme 3A). As an example of further transformations from product 3aa, the activated -CH2- group by the sulfonyl and the tetrazole could undergo nucleophilic substitution and condensation reaction with the assistance of bases (Scheme 3B). The excellent E-selectivity of compound 5 was confirmed by X-ray diffraction, which might be attributed to the π-π stacking interaction of aromatic rings.
Control Experiments and Mechanistic Studies

To confirm the reaction mechanism as described in Scheme 1C, 1.5 equiv 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added as a radical scavenger to the reaction of cycloketone oxime esters 1d, 1-ethynyl-4-methoxybenzene 2a, DABCO$\cdot$(SO$_2$)$_2$, and trimethylsilyl azide under the standard conditions (Scheme 4A). The sulfonylated tetrazole 3da was isolated in 24% yield, and the radical trapping product 6 was obtained in 15% yield. Additionally, the corresponding product 3da was not observed when the amount of TEMPO was increased to 3.0 equiv, revealing that a radical process might be involved in this transformation. Interestingly, two tetrazole isomers 3ax and 3ax$'$ were isolated in 26% and 12% yield with the utilization of 4-ethynyl benzonitrile as the substrate, which implied a competitive migration in this transformation (Scheme 4B). In comparison, we found that most aryl alkenes bearing electron-withdrawing groups (ester, nitro, carbonyl) showed inferior regioselectivity than that of alkenes with electron-donating group in the reaction, possibly because of difficulty of the rearrangement process.

On the basis of the above observation and previous reports (Gaydou and Echavarren, 2013; Qin et al., 2016; Xiang et al., 2017), a plausible mechanism is depicted in Scheme 5. We reasoned that initially, Fe(II)-mediated single-electron reduction of cycloketone oxime ester 1d, 1-ethynyl-4-methoxybenzene 2a, DABCO$\cdot$(SO$_2$)$_2$, and trimethylsilyl azide under the standard conditions (Scheme 4A). The sulfonylated tetrazole 3da was isolated in 24% yield, and the radical trapping product 6 was obtained in 15% yield. Additionally, the corresponding product 3da was not observed when the amount of TEMPO was increased to 3.0 equiv, revealing that a radical process might be involved in this transformation. Interestingly, two tetrazole isomers 3ax and 3ax$'$ were isolated in 26% and 12% yield with the utilization of 4-ethynyl benzonitrile as the substrate, which implied a competitive migration in this transformation (Scheme 4B). In comparison, we found that most aryl alkenes bearing electron-withdrawing groups (ester, nitro, carbonyl) showed inferior regioselectivity than that of alkenes with electron-donating group in the reaction, possibly because of difficulty of the rearrangement process.
through intramolecular C-C bond cleavage leading to alkyl radical D, which would be trapped by sulfur dioxide to provide the sulfonyl radical E. Then, the resulting radical E would attack the triple bond of alkyne 2 to afford alkynyl radical F. Meanwhile, ligand exchange would occur between Fe (III) species A and trimethylsilyl azide providing Fe (III) species B, which would undergo azide group transfer with the alkynyl radical D to deliver the sulfone-containing alkynyl azide intermediate G, with the regeneration of Fe(II) species. Further protonation of intermediate G would offer azide cation intermediate H, which could convert to nitrilium cation intermediate I by migration of R2 group with the release of nitrogen. Finally, the [3 + 2] cycloaddition reaction of intermediate I with trimethylsilyl azide would take place, giving rise to the desired compound 3 (path a). Presumably, if the R2 group was substituted by electron-withdrawing group, a competitive migration of sulfonyl-substituted methylene (path b) would occur and produce intermediate J that is more stable than intermediate I (path a), which might explain the formation of isomers 3ax and 3ax'.

Conclusion

We have demonstrated an efficient five-component reaction of cycloketone oxime esters, alkynes, DABCO-(SO2)2, and two molecules of trimethylsilyl azide under iron catalysis, giving rise to a range of sulfonlated tetrazoles in moderate to good yields. This transformation works effectively with a wide range of substrates, and this multicomponent reaction exhibits excellent selectivity and enables the formation of multiple new chemical bonds in one pot. A possible mechanism involving azidosulfonylation of alkynes, C-C bond cleavage of both cycloketone oxime esters and alkynes, and [3 + 2] cycloaddition of trimethylsilyl azide and the nitrilium cation intermediates is proposed. The radical azidosulfonylation of alkynes enables the formation of sulfone-containing alkynyl azide intermediates, which are essential to form tetrazoles. To our knowledge, this is the first example of terminal alkynes acting as powerful synthons for the synthesis of...
tetrazoles in a radical initiated process. From the synthetic point of view, the advantages including mild conditions, low-cost catalyst, and high-value products make this protocol practical and attractive.

Limitations of the Study
In our current work, aliphatic alkynes and internal alkyne were not suitable substrates for this transformation. Specific cycloketone oxime ester substrates limit the wide application of this methodology.

Resource Availability
Lead Contact
Further information and requests for resources should be directed to and will be fulfilled by the Lead Contact, Jie Wu (jie_wu@fudan.edu.cn).

Materials Availability
This study generated new unique reagents, sulfonylated tetrazoles.

Data and Code Availability
The data for the X-ray crystallographic coordinates for structures reported in this paper have been deposited at the Cambridge Crystallographic Data Centre under accession numbers (CCDC for 3ah: 2005594; CCDC for S: 2042215). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

METHODS
All methods can be found in the accompanying Transparent Methods supplemental file.
SUPPLEMENTAL INFORMATION
Supplemental Information can be found online at https://doi.org/10.1016/j.isci.2020.101872.

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AUTHOR CONTRIBUTIONS
J.Z. conceived the study. J.Z. and X.W. conducted the experiments and analyzed the data. J.W. and Y.K. directed the project. J.Z. prepared the manuscript and Supplemental Information with input from all authors. All authors discussed the results and commented on the manuscript.

DECLARATION OF INTERESTS
The authors declare no competing interests.

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Supplemental Information

Generation of Sulfonylated Tetrazoles through an Iron-Catalyzed Multicomponent Reaction Involving Sulfur Dioxide

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Supplemental Information

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Table S1. Optimization of Conditions, Related to Scheme 2.

| Entry | [M]       | Solvent | T     | Yield(%)b |
|-------|-----------|---------|-------|-----------|
| 1     | Cu(OAc)₂  | CH₃CN   | 60°C  | trace     |
| 2     | Co(OAc)₂  | CH₃CN   | 60°C  | 15        |
| 3     | Fe(OAc)₂  | CH₃CN   | 60°C  | 54        |
| 4     | FeBr₂      | CH₃CN   | 60°C  | 56        |
| 5     | FeCl₂      | CH₃CN   | 60°C  | 58        |
| 6     | FeCl₃      | CH₃CN   | 60°C  | 56        |
| 7     | Fe(OTf)₂   | CH₃CN   | 60°C  | 62        |
| 8     | Fe(OTf)₂   | 1,4-dioxane | 60°C | n.r.       |
| 9     | Fe(OTf)₂   | DCE     | 60°C  | 21        |
| 10    | Fe(OTf)₂   | DMF     | 60°C  | 30        |
| 11    | Fe(OTf)₂   | CH₃CN   | 40°C  | 53        |
| 12    | Fe(OTf)₂   | CH₃CN   | 80°C  | 59        |
| 13c   | Fe(OTf)₂   | CH₃CN   | 60°C  | 56        |

aConditions: cyclobutanone O-(4-(trifluoromethyl)benzoyl) oxime 1a (0.3 mmol), DABCO-(SO₂)₂ (0.2 mmol), TMSN₃ (0.6 mmol), 1-ethynyl-4-methoxybenzene 2a (0.2 mmol), [M] (20 mol %), CH₃CN (2.0 mL), 60°C, N₂, 12 h. b Isolated yield based on 1-ethynyl-4-methoxybenzene 2a. c In the presence of 10 mol % of Fe(OTf)₂.

2. Transparent method

2.1 General information:

Unless otherwise stated, all commercial reagents were used as received. All solvents were dried and distilled according to standard procedures. Flash column chromatography was performed using silica gel (60-Å pore size, 32–63μm, standard grade). Analytical thin–layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~20 Torr at 25–35°C. Nuclear magnetic resonance (NMR) spectra are recorded in parts per million from internal tetramethylsilane on the δ scale. ¹H,¹³C and ¹⁹F NMR spectra were recorded in DMSO-d₆, CDCl₃ or Acetone-d₆ on a Bruker DRX-400 spectrometer operating at 400 MHz, 100 MHz and 376 MHz, respectively. Melting points are tested automatically on a Melting Point Apparatus produced by Shanghai JINGMI Scientific Instruments Co., Ltd. All chemical shift values are quoted in ppm and coupling constants quoted in Hz. High resolution mass spectrometry (HRMS) spectra were obtained on a micrOTOF II Instrument.
2.2 Experimental procedures

Experimental procedure for the synthesis of cycloketone oxime esters 1

**Step 1**: To a mixture of ketone (10 mmol, 1.0 equiv.) and hydroxylamine hydrochloride (11 mmol, 1.1 equiv.) were added sat. Na$_2$CO$_3$ (20 mL). The resulting mixture was stirred at 40 °C overnight. After extraction with ethyl acetate, the solution dried over Na$_2$SO$_4$, and evaporated to provide crude products which were used in the next step without further purification.

**Step 2**: p-CF$_3$ Benzoyl chloride (1.5 equiv.) was added to a mixture of cyclobutanone oxime (1.0 equiv.), triethylamine (2.0 equiv.) and DCM (0.5 M) in a 50 mL round-bottom flask at 0 °C. After stirring for 6 h, water was added and the mixture was stirred for a few more minutes. Then the mixture was diluted with DCM. The organic layer was washed with brine and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was purified directly by column chromatography with n-hexane/EtOAc as an eluent to give cycloketone oxime ester. The products 1a, 1g, 1h, 1i, 1l and 1m (Yu et al., 2018a) are known compounds.

**Step 3**: Alkene (10.0 mmol, 1.0 equiv.), zinc-copper couple (30 mmol, 3.0 equiv.), and anhydrous ether (0.5 M) were added to a round-bottom flask (50 mL). Then a mixed solution of phosphorus oxychloride (11 mmol, 1.1 equiv.) and trichloroacetyl chloride (20 mmol, 2.0 equiv.) in ether (0.5 M) was added dropwise through an addition funnel in 1h. The resulting solution was refluxed overnight. After completion of the starting material as indicated by TLC, the mixture was filtered through a pad of celite and the celite pad was washed with ether (40 mL). The organic solution was successively washed with water (2 x 30 mL), sat. NaHCO$_3$ (2 x 30
mL) and brine (2 x 30 mL), and dried over Na₂SO₄. Then the solution was filtered, concentrated and used in the next step without further purification.

**Step 2:** A mixture of the corresponding 2,2-dichloro-3-substituted cyclobutanone (1.0 equiv.) and zinc powder (4.0 equiv.) in acetic acid (20 mL) was stirred at room temperature for 2 h, which was followed by heating to 80 °C for 5 h. After the scheduled time, the suspension was cooled to room temperature, then water and ether was added to the above solution for extraction. The organic layer was washed successively with sat. NaHCO₃, water and brine, and dried over Na₂SO₄. The solvent was concentrated under reduced pressure. The crude material was then purified by flash chromatography (n-hexane/ethyl acetate) to afford the corresponding 3-substituted cyclobutanone.

**Step 3:** A mixture of 3-substituted cyclobutanone (1.0 equiv.) and hydroxylamine hydrochloride (2.0 equiv.) in pyridine (0.5 M) was stirred at room temperature for 2 hours. Then pyridine was removed under reduced pressure, and the residue was diluted with water and extracted with ethyl acetate. The combined organic phase was washed with brine and dried over Na₂SO₄. The solvent was concentrated under reduced pressure to provide crude product, which was used in the next step without further purification.

**Step 4:** p-CF₃ Benzoyl chloride (1.5 equiv.) was added to a mixture of cyclobutanone oxime (1.0 equiv.), triethylamine (2.0 equiv.) and DCM (0.5 M) in a round-bottom flask at 0 °C. After stirring for 6 h, water was added and the mixture was stirred for a few more minutes. Then the resulting mixture was diluted with DCM. The organic layer was separated, washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure, and the residue was purified directly by column chromatography with n-hexane/EtOAc as eluent to give the 3-substituted cycloketone oxime ester as white solid. The products 1b, 1c, 1d, 1e and 1f (Yu et al., 2018a) are known compounds.

**Step 1:** To a flask (100 mL) equipped with a stirrer, cyclobutanone (10 mmol, 1.0 equiv.) and hydroxylamine hydrochloride (11 mmol, 1.1 equiv.) were added. Then sat. Na₂CO₃ (20 mL) was added and the resulting mixture was stirred at 40 °C overnight. After extraction with ether, the combined organic phase was dried over Na₂SO₄, and concentrated to provide crude product which was used in the next step without further purification.

**Step 2:** n-BuLi (2.0 equiv.) was added slowly to the solution of cyclobutanone oxime (1.0 equiv.) in THF (0.5 M) at 0 °C. Then the mixture was continued to stir for another 15 min at this temperature. After that, RBr (1.0 equiv.) was added dropwise, then the mixture was warmed to room temperature and stirred for another 2 h. Subsequently, cold water and ethyl acetate were successively added to the above solution. The organic layer was separated, washed with water, and dried over Na₂SO₄. The solvent was concentrated under reduced pressure, and the residue was purified by column chromatography (n-hexane/EtOAc) to give 2-substituted cyclobutanone oxime.
**Step 3:** To a mixture of 2-substituted cyclobutanone oxime (1.0 equiv.), triethylamine (1.5 equiv.) and DCM (0.5 M) in a round-bottom flask (50 mL) was added p-CF<sub>3</sub> benzoyl chloride (1.1 equiv.) dropwise at 0 °C. After 3 h, sat. NaHCO<sub>3</sub> was added to the mixture, and the mixture was diluted with DCM. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography (n-hexane/EtOAc) to give 2-substituted cycloketone oxime ester. The products 1j and 1k (Ai et al., 2018) are known compounds.

**Experimental procedure for the synthesis of alkynes 2u and 2v.**

**Step 1:** Triethylamine (12 mmol, 2 equiv.) and trifluoromethanesulfonic anhydride (13.2 mmol, 2.2 equiv.) were added to the solution of phenol (6 mmol, 1.0 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (50 ml) at 0 °C. The mixture was continued to stir for 30 min at this temperature. Subsequently, water (50 ml) were added to the above solution and do an extraction. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 30 ml). The combined organic phase was successively washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to provide crude product, which was purified by column chromatography to give aryl trifluoromethanesulfonate.

**Step 2:** To a mixture of aryl trifluoromethanesulfonate (1.0 equiv.), Pd(PPh<sub>3</sub>Cl<sub>2</sub>) (10 mol%), CuI (10 mol%), triethylamine (3 equiv.) and DMF (0.1 M) in a round-bottom flask was added TMSA (5.0 equiv.) slowly. Then the flask was backfilled with nitrogen three times and stirred at 80 °C for 4 h. After completion as monitored by TLC, water and ethyl acetate were successively added to the above solution and do an extraction. The organic layer was separated, washed with brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (n-hexane/EtOAc) to afford trimethyl(arylethynyl)silane.

**Step 3:** K<sub>2</sub>CO<sub>3</sub> (2.0 equiv.) was added to the mixture of trimethyl(arylethynyl)silane (1.0 equiv.) in MeOH (0.1 M). The mixture was stirred at room temperature for 4 h. After that, the mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography (n-hexane/EtOAc) to afford arylalkynes. The products 2u (Zhang et al., 2014) and 2v (Breed et al., 2009) are known compounds.

**General experimental procedure for the reaction of cycloketone oxime esters 1, alkynes 2, DABCO·(SO<sub>2</sub>)<sub>2</sub>, and TMSN<sub>3</sub>, Related to Scheme 2 and Scheme 4.**

TMSN<sub>3</sub> (0.6 mmol) was added to a mixture of cycloketone oxime ester 1 (0.3 mmol), DABCO·(SO<sub>2</sub>)<sub>2</sub> (0.2 mmol), alkyne 2 (0.2 mmol) and Fe(OTf)<sub>2</sub> (0.04 mmol, 20 mol %) in CH<sub>3</sub>CN under N<sub>2</sub> atmosphere. The resulting mixture was stirred at 60 °C for 12 hours. After completion of reaction as indicated by TLC, sat. NaHCO<sub>3</sub> (20 ml) and ethyl acetate (15 mL) was added for extraction. Subsequently, the combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The aqueous waste was
treated with aqueous NaClO to decompose the N₃-specie. The crude product was purified directly by flash column chromatography to give the corresponding product 3.

Scaled-up version of the model reaction and transformations of the product, Related to Scheme 3.

To a 100 mL round-bottom flask, cycloketone oxime ester 1a (4.5 mmol, 1.16 g), DABCO·(SO₂)₂ (3 mmol, 732 mg) and Fe(OTf)₂ (0.6 mmol, 300 mg) were added. Then the flask was sealed with a rubber stopper and backfilled with nitrogen three times. The solvent MeCN (30 ml), 1-ethynyl-4-methoxybenzene (3 mmol, 396.5 mg) and TMSN₃ (9 mmol, 1.04 g) were injected sequentially. The mixture was stirred at 60°C for 12 h. Upon completion, sat. NaHCO₃ (30 ml) was added. Next, the most organic solvent was evaporated and ethyl acetate (30 mL) were added for extraction. The organic layer was successively washed with sat. NaHCO₃ (30 mL) and brine (30 mL), and dried over Na₂SO₄. The solution was filtered, concentrated and the residue was purified directly by flash column chromatography (n-hexane/ethyl acetate = 3:1-1:1) to give the corresponding product 3aa (561.4 mg, 58% yield), and the aqueous waste was treated with aqueous NaClO to decompose the N₃-specie.

To a solution of 3aa (64.3 mg, 0.2 mmol) in dried THF (2.0 mL, 0.1 M) was added a solution of NaHMDS in THF (2M, 0.12 mL) dropwise at 0°C. After stirring for 10 minutes, the allyl bromide (48.4 mg, 0.4 mmol) was added. The resulting mixture was stirred at room temperature for 6 h and then quenched with H₂O, extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (n-hexane/ethyl acetate = 3/1) to give compound 4 (colorless oil, 42.0 mg, 58%).

A sealed tube was charged with 3aa (48.2 mg, 0.15 mmol), followed by benzaldehyde (17.0 mg, 0.16 mmol), piperidine (about 10 mol%), and acetic acid (about 10 mol%). The resulting solution heated to reflux. After stirred for 4h, the mixture was purified by silica gel column chromatography directly (n-hexane/ethyl acetate = 3/1) to give compound 5 (white solid, 57.2 mg, 70%).

3. Data S1. The characterization of 3, 4, 5 and 6, Related to Scheme 2, Scheme 3 and Scheme 4.
4-(((1-(4-Methoxyphenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3aa); yield: 39.6 mg (62%); white solid; m.p.: 93.3-95.0 °C. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.50 (d, J = 8.9 Hz, 2H), 7.09 (d, J = 8.9 Hz, 2H), 4.61 (s, 2H), 3.90 (s, 3H), 3.66-3.51 (m, 2H), 2.66 (t, J = 7.1 Hz, 2H), 2.38-2.23 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 161.6, 146.2, 127.2, 124.9, 118.1, 115.2, 55.7, 50.6, 47.4, 18.1, 16.1. HRMS (ESI) calcd for C₁₃H₁₅N₅NaO₃S⁺: 344.0788 (M+Na⁺), found: 344.0791.

4-(((1-(4-Ethoxyphenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3ab); yield: 43.0 mg (64%); white solid; m.p.: 128.8-130.2 °C. ¹H NMR (400 MHz, Acetone-d₆) δ (ppm) 7.62 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.3 Hz, 2H), 4.96 (s, 2H), 4.20 (q, J = 6.8 Hz, 2H), 3.60 (t, J = 7.6 Hz, 2H), 2.78 (t, J = 7.1 Hz, 2H), 2.31-2.24 (m, 2H), 1.44 (t, J = 6.8 Hz, 3H). ¹³C NMR (100 MHz, Acetone-d₆) δ (ppm) 160.9, 147.0, 127.5, 125.7, 118.7, 115.4, 63.9, 51.1, 47.2, 18.4, 15.4, 14.1. HRMS (ESI) calcd for C₁₄H₁₈N₅O₃S⁺: 336.1125 (M+H⁺), found: 336.1127.

4-(((1-(4-(Trifluoromethoxy)phenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3ac); yield: 32.2 mg (43%); white solid; m.p.: 87.1-88.3 °C. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.80-7.58 (m, 2H), 7.48 (d, J = 8.5 Hz, 2H), 4.64 (s, 2H), 3.70-3.48 (m, 2H), 2.67 (t, J = 7.1 Hz, 2H), 2.41-2.21 (m, 2H). ¹⁹F NMR (376 MHz, CDCl₃) δ (ppm) -57.83 (s). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 151.1, 146.2, 130.7, 127.6, 122.4, 120.2 (d, JCF = 259.4 Hz), 118.0, 50.6, 47.5, 18.2, 16.2. HRMS (ESI) calcd for C₁₃H₁₃F₃N₅O₃S⁺: 376.0686 (M+H⁺), found: 376.0672.

4-(((1-(Phenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3ad); yield: 36.5 mg (63%); white solid; m.p.: 117.1-118.2 °C. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm) 7.74-7.54 (m, 5H), 5.13 (s, 2H), 3.60-3.38 (m, 2H), 2.66 (t, J = 7.2 Hz, 2H), 2.14-1.88 (m, 2H). ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm) 146.9, 133.3, 131.3, 130.3, 126.0, 120.0, 51.3, 47.2, 18.0, 15.5. HRMS (ESI) calcd for C₁₃H₁₄N₅O₂S⁺: 292.0863 (M+H⁺), found: 292.0861.
4-(((1-(p-Tolyl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3ae); yield: 39.2 mg (64%); white solid; m.p.: 116.4-116.6 °C. ^1H NMR (400 MHz, DMSO-d6) δ (ppm) 7.57 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H), 5.11 (s, 2H), 3.49 (t, J = 7.7 Hz, 2H), 2.68 (t, J = 7.1 Hz, 2H), 2.44 (s, 3H), 2.16 – 1.93 (m, 2H). ^13C NMR (100 MHz, DMSO-d6) δ (ppm) 147.0, 141.4, 130.9, 130.8, 125.9, 120.1, 51.5, 47.3, 21.3, 18.2, 15.7. HRMS (ESI) calcd for C_{13}H_{16}N_{2}O_{2}S: 306.1019 (M+H+), found: 306.1027.

![Structure of 3ae](image)

4-(((1-(4-Ethylphenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3af); yield: 38.3 mg (60%); white solid; m.p.: 53.3-54.8 °C. ^1H NMR (400 MHz, CDCl3) δ (ppm) 7.51 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 5.24 (t, J = 7.3 Hz, 2H), 4.66 (s, 2H), 2.97 (q, J = 7.5 Hz, 2H), 2.68 (t, J = 7.1 Hz, 2H), 2.38 – 2.60 (m, 2H), 1.12 (t, J = 7.3 Hz, 3H). ^13C NMR (100 MHz, CDCl3) δ (ppm) 148.2, 146.0, 130.1, 129.7, 125.6, 118.0, 50.7, 47.6, 28.7, 18.3, 16.3, 15.2. HRMS (ESI) calcd for C_{18}H_{18}N_{2}O_{2}S: 320.1176 (M+H+), found: 320.1181.

![Structure of 3af](image)

4-(((1-(4-(tert-Butyl)phenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3ag); yield: 37.4 mg (54%); white solid; m.p.: 100.5-102.5 °C. ^1H NMR (400 MHz, CDCl3) δ (ppm) 7.63 (d, J = 8.1 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 4.62 (s, 2H), 3.61 (t, J = 7.3 Hz, 2H), 2.67 (t, J = 7.0 Hz, 2H), 2.39 – 2.28 (m, 2H), 1.97 (m, 2H), 1.39 (s, 9H). ^13C NMR (100 MHz, CDCl3) δ (ppm) 155.0, 146.0, 129.8, 127.2, 125.2, 118.0, 50.6, 47.5, 35.0, 31.1, 18.2, 16.2. HRMS (ESI) calcd for C_{18}H_{22}N_{2}O_{2}S: 348.1489 (M+H+), found: 348.1492.

![Structure of 3ag](image)

4-(((1,1'-Biphenyl)-4-yl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3ah); yield: 27.0 mg (37%); pale yellow solid; m.p.: 168.5-169.7 °C. ^1H NMR (400 MHz, DMSO-d6) δ (ppm) 7.98 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 7.8 Hz, 2H), 7.54 (t, J = 7.5 Hz, 2H), 7.46 (t, J = 7.2 Hz, 1H), 5.20 (s, 2H), 3.59 – 3.44 (m, 2H), 2.70 (t, J = 7.1 Hz, 2H), 2.21 – 1.97 (m, 2H). ^13C NMR (100 MHz, DMSO-d6) δ (ppm) 147.1, 143.0, 139.0, 132.6, 129.6, 128.8, 128.6, 127.5, 126.6, 120.1, 51.5, 47.4, 18.2, 15.7. HRMS (ESI) calcd for C_{18}H_{18}N_{2}O_{2}S: 368.1176 (M+H+), found: 368.1179.

![Structure of 3ah](image)

4-(((1-(4-Dimethylamino)phenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3ai); yield: 26.5 mg (40%); pale yellow solid; m.p.: 121.8-123.1 °C. ^1H NMR (400 MHz, Acetone-d6) δ (ppm) 7.47 (d, J = 8.3 Hz, 2H), 6.92 (d, J = 8.3 Hz, 2H), 4.91 (s, 2H), 3.59 (t, J = 7.6 Hz, 2H), 3.09 (s, 6H), 2.78 (t, J = 7.5 Hz, 2H), 2.32 – 2.23 (m, 2H). ^13C NMR (100 MHz, Acetone-d6) δ (ppm) 151.9, 146.9, 126.6, 121.1, 118.7, 111.9, 51.0, 47.1, 39.4, 18.3, 15.3. HRMS (ESI) calcd for C_{18}H_{18}N_{2}O_{2}S: 357.1104 (M+Na+), found: 357.1113.
4-(((1-(4-Fluorophenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3aj); yield: 37.9 mg (61%); white solid; m.p.: 88.2-89.6 °C. 1H NMR (400 MHz, DMSO-d6) δ (ppm) 7.82 – 7.69 (m, 2H), 7.52 (t, J = 8.6 Hz, 2H), 5.13 (s, 2H), 3.49 – 3.44 (m, 2H), 2.66 (t, J = 7.1 Hz, 2H), 2.07 – 1.98 (m, 2H). 19F NMR (376 MHz, DMSO-d6) δ (ppm) -109.65 – -109.85 (m). 13C NMR (100 MHz, DMSO-d6) δ (ppm) 163.4 (d, JCF = 248.6 Hz), 147.2, 129.6, 128.8 (d, JCF = 9.4 Hz), 120.0, 117.3 (d, JCF = 23.5 Hz), 51.3, 47.0, 18.0, 15.5. HRMS (ESI) calcd for C12H13FN3O2S+: 310.0768 (M+H+), found: 310.0769.

4-(((1-(4-Chlorophenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3ak); yield: 26.7 mg (40%); white solid; m.p.: 124.5-125.6 °C. 1H NMR (400 MHz, DMSO-d6) δ (ppm) 7.83 – 7.69 (m, 4H), 5.18 (s, 2H), 3.49 (t, J = 7.7 Hz, 2H), 2.69 (t, J = 7.1 Hz, 2H), 2.15 – 1.96 (m, 2H). 13C NMR (100 MHz, DMSO-d6) δ (ppm) 147.2, 136.1, 132.3, 130.5, 128.1, 120.1, 51.5, 47.2, 18.1, 15.7. HRMS (ESI) calcd for C12H13ClN3O2S+: 326.0473 (M+H+), found: 326.0480.

4-(((1-(4-Bromophenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3al); yield: 31.0 mg (42%); white solid; m.p.: 143.8-145.2 °C. 1H NMR (400 MHz, DMSO-d6) δ (ppm) 7.90 (d, J = 8.1 Hz, 2H), 7.67 (d, J = 8.1 Hz, 2H), 5.18 (s, 2H), 3.49 (t, J = 7.5 Hz, 2H), 2.69 (t, J = 7.0 Hz, 2H), 2.16 – 1.98 (m, 2H). 13C NMR (100 MHz, DMSO-d6) δ (ppm) 147.2, 133.4, 132.7, 128.3, 124.8, 120.1, 51.5, 47.17, 18.1, 15.7. HRMS (ESI) calcd for C12H13BrN3O2S+: 369.9968 (M+H+), found: 369.9979.

Methyl 4-((5-((3-cyanopropyl)sulfonyl)methyl)-1H-tetrazol-1-yl)benzoate (3am); yield: 23.7 mg (34%); white solid; m.p.: 152.4-154.2 °C. 1H NMR (400 MHz, Acetone-d6) δ (ppm) 8.31 (d, J = 8.3 Hz, 2H), 7.92 (d, J = 8.3 Hz, 2H), 5.11 (s, 2H), 3.98 (s, 3H), 3.60 (t, J = 7.6 Hz, 2H), 2.78 (t, J = 7.2 Hz, 2H), 2.33 – 2.22 (m, 2H). 13C NMR (100 MHz, Acetone-d6) δ (ppm) 165.2, 146.9, 137.0, 132.44, 131.0, 126.0, 118.6, 52.0, 51.2, 47.2, 18.3, 15.4. HRMS (ESI) calcd for C14H17N5O3S+: 350.0918 (M+H+), found: 350.0912.
4-(((1-(m-Tolyl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3an); yield: 32.5 mg (53%); white solid; m.p.: 62.2-64.2 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.54 – 7.43 (m, 2H), 7.41-7.35 (m, 2H), 4.62 (s, 2H), 3.60 (t, $J = 7.4$ Hz, 2H), 2.67 (t, $J = 7.1$ Hz, 2H), 2.47 (s, 3H), 2.37 -2.27 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 145.9, 140.7, 132.4, 132.1, 129.9, 126.1, 122.6, 118.0, 50.6, 47.5, 21.2, 18.2, 16.2. HRMS (ESI) calcd for C$_{13}$H$_{18}$N$_2$O$_2$S$: 306.1019 (M+H$^+$), found: 306.1029.

4-(((1-(o-Tolyl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3ao); yield: 40.7 mg (67%); pale yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.55 (td, $J = 7.6$, 1.3 Hz, 1H), 7.48 – 7.40 (m, 2H), 7.35 (dd, $J = 7.8$, 1.2 Hz, 1H), 4.52 (s, 2H), 3.72 – 3.49 (m, 2H), 2.65 (t, $J = 7.1$ Hz, 2H), 2.43 – 2.18 (m, 2H), 2.08 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 146.7, 135.8, 131.9, 131.7, 131.3, 127.4, 127.2, 118.0, 50.6, 47.2, 18.2, 17.2, 16.1. HRMS (ESI) calcd for C$_{13}$H$_{18}$N$_2$O$_2$S$: 306.1019 (M+H$^+$), found: 306.1000.

4-(((1-(Naphthalen-1-yl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3ap); yield: 21.3 mg (31%); pale yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.16 (d, $J = 8.0$ Hz, 1H), 8.03 (d, $J = 8.1$ Hz, 1H), 7.76 – 7.53 (m, 4H), 7.10 (d, $J = 8.5$ Hz, 1H), 4.45 (s, 2H), 3.61 (dd, $J = 14.6$, 7.1 Hz, 2H), 2.72 – 2.56 (m, 2H), 2.38 – 2.21 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 147.6, 134.1, 132.4, 128.8, 128.8, 128.7, 128.1, 127.7, 126.2, 125.2, 121.1, 117.9, 50.7, 47.4, 18.2, 16.2. HRMS (ESI) calcd for C$_{16}$H$_{16}$N$_2$O$_2$S$: 342.1019 (M+H$^+$), found: 342.1027.

4-(((1-(Naphthalen-2-yl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3aq); yield: 23.7 mg (35%); white solid; m.p.: 128.4-129.2 °C. $^1$H NMR (400 MHz, Acetone-d$_6$) $\delta$ (ppm) 8.34 (d, $J = 1.9$ Hz, 1H), 8.23 (d, $J = 8.8$ Hz, 1H), 8.15 – 8.05 (m, 2H), 7.81 – 7.67 (m, 3H), 5.13 (s, 2H), 3.66 – 3.58 (m, 2H), 2.77 (t, $J = 7.2$ Hz, 2H), 2.31 – 2.24 (m, 2H). $^{13}$C NMR (100 MHz, Acetone-d$_6$) $\delta$ (ppm) 147.1, 133.9, 133.0, 130.8, 130.2, 128.7, 128.2, 128.1, 127.7, 125.2, 122.9, 118.6, 51.2, 47.3, 18.4, 15.4. HRMS (ESI) calcd for C$_{16}$H$_{16}$N$_2$O$_2$S$: 342.1019 (M+H$^+$), found: 342.1012.
4-(((1-(4,4-Dimethylthiochroman-6-yl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3ar); yield: 39.0 mg (50%); yellow oil. \( ^1H \) NMR (400 MHz, CDCl\( _3 \)) \( \delta \) (ppm) 7.62 (d, \( J = 2.3 \) Hz, 1H), 7.30 – 7.20 (m, 2H), 4.57 (s, 2H), 3.71 – 3.50 (m, 2H), 3.13 – 3.05 (m, 2H), 2.68 (t, \( J = 7.2 \) Hz, 2H), 2.38 – 2.31 (m, 2H), 2.02 – 1.96 (m, 2H), 1.36 (s, 6H). \( ^{13}C \) NMR (100 MHz, CDCl\( _3 \)) \( \delta \) (ppm) 145.9, 144.1, 137.3, 128.1, 127.9, 123.9, 122.8, 117.9, 50.6, 47.6, 36.4, 33.4, 29.8, 23.1, 18.2, 16.2. HRMS (ESI) calcd for C\(_{17}\)H\(_{22}\)N\(_5\)O\(_2\)S\(_2\)+: 392.1209 (M+H\(^+\)), found: 392.1219.

4-(((1-Cyclohex-1-en-1-yl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3as); yield: 30.0 mg (51%); yellow oil. \( ^1H \) NMR (400 MHz, CDCl\( _3 \)) \( \delta \) (ppm) 6.30 – 6.10 (m, 1H), 4.66 (s, 2H), 3.58 – 3.48 (m, 2H), 2.66 (t, \( J = 7.1 \) Hz, 2H), 2.54 – 2.45 (m, 2H), 2.38 – 2.24 (m, 4H), 1.95 – 1.84 (m, 2H), 1.78 – 1.72 (m, 2H). \( ^{13}C \) NMR (100 MHz, CDCl\( _3 \)) \( \delta \) (ppm) 145.1, 132.5, 129.6, 118.0, 50.5, 47.6, 28.5, 24.5, 22.0, 20.8, 18.4, 16.1. HRMS (ESI) calcd for C\(_{12}\)H\(_{18}\)N\(_5\)O\(_2\)S\(_2\)+: 296.1176 (M+H\(^+\)), found: 296.1177.

4-(((1-Thiophen-3-yl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3at); yield: 31.5 mg (53%); white solid; m.p.: 195.2-196.7 °C. \( ^1H \) NMR (400 MHz, Acetone-d\(_6 \)) \( \delta \) (ppm) 8.06 (d, \( J = 8.4 \) Hz, 1H), 7.87 (s, 1H), 7.69 (d, \( J = 8.3 \) Hz, 1H), 6.58 (s, 1H), 5.27 (s, 2H), 5.06 (s, 2H), 3.50 – 3.45 (m, 2H), 2.67 (t, \( J = 6.9 \) Hz, 2H), 2.07 – 1.99 (m, 2H), 1.79 (t, \( J = 7.1 \) Hz, 2H), 2.35 – 2.24 (m, 2H). \( ^{13}C \) NMR (100 MHz, Acetone-d\(_6 \)) \( \delta \) (ppm) 159.6, 153.5, 153.0, 147.2, 147.0, 142.5, 127.5, 122.0, 121.8, 120.1, 116.3, 114.4, 51.4, 47.15, 18.6, 18.0, 15.6. HRMS (ESI) calcd for C\(_{10}\)H\(_{12}\)N\(_5\)O\(_2\)S\(_2\)+: 298.0427 (M+H\(^+\)), found: 298.0428.

4-(((1-(4-Methyl-2-oxo-2H-chromen-7-yl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3au); yield: 22.7 mg (33%); pale-yellow solid; m.p.: 185.1-187.0 °C. \( ^1H \) NMR (400 MHz, DMSO-d\(_6 \)) \( \delta \) (ppm) 8.06 (d, \( J = 8.4 \) Hz, 1H), 7.87 (s, 1H), 7.69 (d, \( J = 8.3 \) Hz, 1H), 6.58 (s, 1H), 5.27 (s, 2H), 3.50 – 3.45 (m, 2H), 2.67 (t, \( J = 6.9 \) Hz, 2H), 2.07 – 1.99 (m, 2H), 1.79 (t, \( J = 7.1 \) Hz, 2H), 2.35 – 2.24 (m, 2H). \( ^{13}C \) NMR (100 MHz, DMSO-d\(_6 \)) \( \delta \) (ppm) 159.6, 153.5, 153.0, 147.2, 147.0, 142.5, 127.5, 122.0, 121.8, 120.1, 116.3, 114.4, 51.4, 47.15, 18.6, 18.0, 15.6. HRMS (ESI) calcd for C\(_{16}\)H\(_{16}\)N\(_5\)O\(_2\)S\(_2\)+: 374.0918 (M+H\(^+\)), found: 374.0915.
4-(((1-((8R,9S,13S,14S)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3av); yield: 48.5 mg (52%); white solid; m.p.: 78.2-80.0 °C. 1H NMR (400 MHz, Acetone-d6) δ (ppm) 7.63 (d, J = 8.1 Hz, 1H), 7.51 – 7.41 (m, 2H), 5.00 (s, 2H), 3.59 (t, J = 7.3 Hz, 2H), 3.04 (d, J = 4.3 Hz, 2H), 2.78 (t, J = 7.0 Hz, 2H), 2.50 (dd, J = 24.5, 14.6 Hz, 3H), 2.32 – 2.22 (m, 2H), 2.19 – 2.04 (m, 3H), 1.92 (d, J = 12.6 Hz, 1H), 1.81 – 1.46 (m, 6H), 0.95 (s, 3H). 13C NMR (100 MHz, Acetone-d6) δ (ppm) 218.4, 146.7, 143.2, 139.0, 130.9, 127.0, 125.8, 122.8, 118.7, 51.0, 50.2, 47.4, 47.2, 44.3, 37.7, 35.1, 31.6, 25.9, 25.4, 21.2, 18.3, 15.3, 13.2. HRMS (ESI) calcd for C24H30N5O3S+: 468.2064 (M+H+), found: 468.2057.

4-(((1-3-(3-((6,7-Bis(2-methoxyethoxy)quinazolin-4-yl)amino)phenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3aw); yield: 52.4 mg (45%); white solid; m.p.: 104.6-105.8 °C. 1H NMR (400 MHz, DMSO-d6) δ (ppm) 9.81 (s, 1H), 8.55 (s, 1H), 8.29 (s, 1H), 8.05 (d, J = 8.1 Hz, 1H), 7.90 (s, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.26 (s, 1H), 5.25 (s, 2H), 4.31 (s, 4H), 3.79 (s, 2H), 3.76 (s, 2H), 3.62 (s, 2H), 2.69 (t, J = 7.0 Hz, 2H), 2.14 – 2.02 (m, 2H). 1H NMR (100 MHz, DMSO-d6) δ (ppm) 218.4, 156.5, 154.3, 153.0, 148.7, 147.2, 147.2, 141.2, 133.3, 129.46, 128.8, 127.6, 124.0, 120.1, 120.0, 119.1, 109.3, 108.4, 103.6, 70.5, 70.5, 68.8, 68.5, 58.8, 58.8, 51.4, 47.4, 18.1, 15.6. HRMS (ESI) calcd for C26H31N8O6S+: 583.2082 (M+H+), found: 583.2075.

4-(((1-(4-Methoxyphenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)-3-phenylbutanenitrile (3ba); yield: 48.1 mg (61%); pale yellow oil. 1H NMR (400 MHz, CDCl3) δ (ppm) 7.46 – 7.32 (m, 7H), 7.05 (d, J = 7.6 Hz, 2H), 4.26 (d, J = 15.3 Hz, 1H), 4.16 (dd, J = 13.8, 6.2 Hz, 1H), 4.02 (d, J = 15.2 Hz, 1H), 3.88 (s, 3H), 3.82 – 3.66 (m, 2H), 2.96 – 2.92 (m, 2H). 13C NMR (100 MHz, CDCl3) δ (ppm) 161.6, 146.1, 137.7, 129.46, 128.8, 127.6, 127.6, 124.0, 117.0, 115.2, 55.7, 48.1, 36.7, 24.4. HRMS (ESI) calcd for C19H20N2O3S+: 398.1281 (M+H+), found: 398.1295.
3-(4-Bromophenyl)-4-(((1-(4-methoxyphenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3ca); yield: 66.4 mg (70%); pale yellow solid; m.p.: 61.8-62.7 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.54 (d, \(J = 8.0\) Hz, 2H), 7.44 (d, \(J = 8.3\) Hz, 2H), 7.30 (d, \(J = 7.9\) Hz, 2H), 7.06 (d, \(J = 8.2\) Hz, 2H), 4.34 (d, \(J = 15.2\) Hz, 1H), 4.20 – 4.04 (m, 2H), 3.89 (s, 3H), 3.76 – 3.62 (m, 2H), 3.04 – 2.80 (m, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 161.6, 146.1, 141.5, 139.8, 136.6, 128.8, 128.0, 127.7, 127.2, 126.9, 124.8, 117.0, 115.2, 55.7, 48.2, 36.4, 24.4. HRMS (ESI) calcd for C\(_{19}\)H\(_{19}\)BrN\(_5\)O\(_3\)S\(^+\): 476.0386 (M+H\(^+\)), found: 476.0388.

3-[1,1'-Biphenyl]-4-yl)-4-(((1-(4-methoxyphenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3da); yield: 54.2 mg (57%); pale yellow solid; m.p.: 139.1-141.0 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.64 – 7.54 (m, 4H), 7.51 – 7.32 (m, 7H), 7.02 (d, \(J = 7.6\) Hz, 2H), 4.29 (d, \(J = 15.3\) Hz, 1H), 4.19 (dd, \(J = 13.9, 6.4\) Hz, 1H), 4.09 (d, \(J = 15.2\) Hz, 1H), 3.88 – 3.69 (m, 5H), 3.05 – 2.85 (m, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 161.5, 146.1, 141.5, 139.8, 136.6, 128.8, 128.0, 127.7, 127.2, 126.9, 124.8, 117.0, 115.2, 55.7, 48.2, 36.4, 24.4. HRMS (ESI) calcd for C\(_{25}\)H\(_{24}\)N\(_5\)O\(_3\)S\(^+\): 474.1590 (M+H\(^+\)), found: 474.1590.

4-(((1-(4-Methoxyphenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)-3-(m-toly)butanenitrile (3ea); yield: 48.6 mg (59%); pale yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.44 (d, \(J = 7.9\) Hz, 2H), 7.32 – 7.13 (m, 4H), 7.05 (d, \(J = 8.0\) Hz, 2H), 4.28 – 4.10 (m, 2H), 3.98 (d, \(J = 15.2\) Hz, 1H), 3.88 (s, 3H), 3.76-3.62 (m, 2H), 3.00 – 2.84 (m, 2H), 2.36 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 161.6, 146.1, 139.4, 137.5, 129.6, 129.3, 128.3, 127.2, 124.9, 124.6, 117.0, 115.2, 55.8, 55.7, 48.1, 36.8, 24.4, 21.4. HRMS (ESI) calcd for C\(_{20}\)H\(_{22}\)N\(_5\)O\(_3\)S\(^+\): 412.1438 (M+H\(^+\)), found: 412.1442.

4-(((1-(4-Methoxyphenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)-3-methyl-3-phenylbutanenitrile (3fa); yield: 46.7 mg (57%); pale yellow solid; m.p.: 48.6-51.3 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.54 (d, \(J = 7.5\) Hz, 2H), 7.45 - 7.35 (m, 4H), 7.32 (t, \(J = 7.2\) Hz, 1H), 7.02 (d, \(J = 8.0\) Hz, 2H), 4.08 (d, \(J = 15.2\) Hz, 1H), 3.93 – 3.77 (m, 5H), 3.71 (d, \(J = 15.3\) Hz, 1H), 3.27 – 3.14 (m, 2H), 1.85 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 161.5, 146.2, 139.9, 129.1, 128.3, 127.2, 126.3,
124.9, 117.0, 115.1, 61.0, 55.7, 48.5, 40.0, 29.1, 26.3. HRMS (ESI) calcd for C_{20}H_{22}N_{5}O_{3}S^{+}: 412.1438 (M+H^{+}), found: 412.1449.

**tert-Butyl 3-cyano-2-(((1-(4-methoxyphenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)methyl)propanoate (3ga); yield: 50.6 mg (60%); pale yellow oil.** $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.49 (d, $J = 8.1$ Hz, 2H), 7.09 (d, $J = 8.1$ Hz, 2H), 4.68 (q, $J = 15.2$ Hz, 2H), 4.12 (dd, $J = 14.5$, 5.9 Hz, 1H), 3.90 (s, 3H), 3.67 (dd, $J = 14.5$, 6.7 Hz, 1H), 3.42–3.25 (m, 1H), 3.02–2.81 (m, 2H), 1.50 (s, 9H).

**13C NMR (100 MHz, CDCl$_3$) δ (ppm) 168.2, 161.6, 146.1, 127.2, 125.0, 116.4, 115.2, 84.2, 55.7, 52.4, 48.5, 36.9, 27.7, 19.6. HRMS (ESI) calcd for C_{18}H_{24}N_{5}O_{3}S^{+}: 422.1493 (M+H^{+}), found: 422.1489.**

**3-(Benzyloxy)-4-(((1-(4-methoxyphenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)butanenitrile (3ha); yield: 50.7 mg (59%); pale yellow oil.** $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.46–7.28 (m, 7H), 7.05 (d, $J = 8.3$ Hz, 2H), 4.82–4.60 (m, 3H), 4.53–4.33 (m, 2H), 4.13–3.97 (m, 1H), 3.88 (s, 3H), 3.54 (d, $J = 15.0$ Hz, 1H), 2.81 (d, $J = 5.3$ Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm) 161.5, 146.2, 135.9, 128.7, 128.5, 128.2, 127.2, 125.0, 116.1, 115.2, 73.0, 70.4, 55.7, 55.2, 49.1, 22.6. HRMS (ESI) calcd for C_{20}H_{22}N_{5}O_{4}S^{+}: 428.1387 (M+H^{+}), found: 428.1384.

**tert-Butyl (1-cyano-3-(((1-(4-methoxyphenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)propan-2-yl)carbamate (3ia); yield: 59.5 mg (68%); pale yellow oil.** $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.51–7.46 (m, 2H), 7.09–7.04 (m, 2H), 5.76 (s, 1H), 4.77–4.65 (m, 3H), 4.39–3.97 (m, 1H), 3.91–3.84 (m, 4H), 3.70–3.62 (m, 1H), 2.92 (d, $J = 5.4$ Hz, 2H), 1.42 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm) 161.6, 154.9, 146.3, 127.3, 124.9, 116.5, 115.3, 81.1, 55.8, 54.4, 48.1, 43.4, 28.2, 23.8. HRMS (ESI) calcd for C_{18}H_{24}N_{5}O_{5}S^{+}: 459.1421 (M+Na^{+}), found: 459.1417.

**4-(((1-(4-Methoxyphenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)hept-6-enenitrile (3ja); yield: 36.1 mg (50%); pale yellow oil.** $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.50 (d, $J = 7.8$ Hz, 2H), 7.09 (d, $J = 7.8$ Hz, 2H), 6.01–5.80 (m, 1H), 5.37–5.26 (m, 2H), 4.69 (d, $J = 15.3$ Hz, 1H), 4.49 (d, $J = 15.2$ Hz, 1H), 3.90 (s, 3H), 3.85–3.74 (m, 1H), 2.92–2.80 (m, 1H), 2.68–2.51 (m, 3H), 2.41–2.28 (m, 1H), 2.26–2.14 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm) 161.6, 146.1, 131.7,
HRMS (ESI) calcd for C_{16}H_{20}N_{5}O_{3}S: 362.1281 (M+H^+), found: 362.1292.

4-(((1-(4-Methoxyphenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)-5-phenylpentanenitrile (3ka); yield: 52.7 mg (64%); pale yellow oil. \(^1H\) NMR (400 MHz, CDCl\(_3\)) δ (ppm) 7.47 (d, \(J = 7.8\) Hz, 2H), 7.43 – 7.35 (m, 4H), 7.34 7.28 (m, 1H), 7.07 (d, \(J = 7.8\) Hz, 2H), 4.42 – 4.29 (m, 2H), 4.15 – 4.04 (m, 1H), 3.89 (s, 3H), 3.51 (dd, \(J = 13.8, 4.8\) Hz, 1H), 3.01 – 2.87 (m, 1H), 2.60 – 2.21 (m, 3H), 2.17 – 2.04 (m, 1H). HRMS (ESI) calcd for C_{20}H_{22}N_{5}O_{3}S: 412.1438 (M+H^+), found: 412.1445.

1H NMR (400 MHz, CDCl\(_3\) δ (ppm) 7.49 (d, \(J = 7.9\) Hz, 2H), 7.09 (d, \(J = 7.9\) Hz, 2H), 4.57 (s, 2H), 3.90 (s, 3H), 3.77 (s, 2H), 3.68 – 3.56 (m, 2H), 3.38 – 3.25 (m, 2H), 2.86 (s, 2H), 1.97 – 1.86 (m, 2H), 1.72 – 1.64 (m, 2H), 1.46 (s, 9H). HRMS (ESI) calcd for C_{22}H_{31}N_{6}O_{5}S: 491.2071 (M+H^+), found: 491.2062.

2-(((1-(4-Methoxyphenyl)-1H-tetrazol-5-yl)methyl)sulfonyl)methoxy)acetonitrile (3ma); yield: 25.7 mg (40%); white solid; m.p.: 122.7-123.7 °C. \(^1H\) NMR (400 MHz, Acetone-d\(_6\)) δ (ppm) 7.63 (d, \(J = 7.6\) Hz, 2H), 7.23 (d, \(J = 7.6\) Hz, 2H), 5.08 (s, 2H), 4.96 (s, 2H), 4.89 (s, 2H), 3.95 (s, 3H), 3.47 – 3.35 (m, 2H), 3.23 – 3.02 (m, 2H), 2.76 – 2.53 (m, 2H), 2.35 - 2.18 (m, 2H). HRMS (ESI) calcd for C_{12}H_{14}N_{6}O_{4}S: 324.0761 (M+H^+), found: 324.0769.

4-((1-(4-Methoxyphenyl)-1H-tetrazol-5-yl)but-3-en-1-yl)sulfonylebutanenitrile (4); yield: 42.0 mg (58%); colorless oil. \(^1H\) NMR (400 MHz, CDCl\(_3\)) δ (ppm) 7.41 (d, \(J = 8.8\) Hz, 2H), 7.08 (d, \(J = 8.8\) Hz, 2H), 5.59 – 5.38 (m, 1H), 5.12 – 5.00 (m, 2H), 4.36 – 4.25 (m, 1H), 3.90 (s, 3H), 3.78 – 3.65 (m, 1H), 3.47 – 3.35 (m, 1H), 3.23 – 3.02 (m, 2H), 2.76 – 2.53 (m, 2H), 2.35 - 2.18 (m,
$^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm) 161.6, 149.8, 130.1, 127.7, 124.8, 121.0, 118.0, 115.2, 59.65, 55.8, 46.8, 33.9, 17.4, 16.4. HRMS (ESI) calcd for C$_{16}$H$_{20}$N$_5$O$_3$S$: 362.1281 (M+H$^+$), found: 362.1298.

$^{	ext{E}}$-4-((1-(1-(4-methoxyphenyl)-1H-tetrazol-5-yl)-2-phenylvinyl)sulfonyl)butanenitrile (5); yield: 57.2 mg (70%); white solid; m.p.: 130.8 - 131.1 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 8.00 (s, 1H), 7.39 (t, $J$ = 7.3 Hz, 1H), 7.29 - 7.19 (m, 2H), 7.01 (d, $J$ = 8.1 Hz, 2H), 6.83 - 6.65 (m, 4H), 3.80 - 3.63 (m, 5H), 2.84 - 2.54 (m, 2H), 2.45 - 2.25 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm) 160.8, 149.6, 147.7, 132.1, 130.5, 129.4, 129.2, 125.8, 125.3, 123.4, 118.1, 114.4, 55.6, 51.5, 19.1, 16.2. HRMS (ESI) calcd for C$_{20}$H$_{20}$N$_5$O$_3$S$: 410.1281 (M+H$^+$), found: 410.1275.

3-(1,1′-Biphenyl)-4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)butanenitrile (6) (Zhang et al., 2020); yield: 11.4 mg (15%); colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.60 - 7.55 (m, 4H), 7.47 - 4.41 (m, 2H), 7.37 - 7.31 (m, 3H), 4.02 (d, $J$ = 6.4 Hz, 2H), 3.27 (dt, $J$ = 12.5, 6.3 Hz, 1H), 2.95 (dd, $J$ = 16.7, 5.8 Hz, 1H), 2.78 (dd, $J$ = 16.7, 8.0 Hz, 1H), 1.55 - 1.27 (m, 6H), 1.16 - 1.06 (m, 12H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm) 140.6, 140.6, 138.3, 128.8, 128.0, 127.4, 127.4, 127.1, 118.7, 78.2, 60.1, 41.7, 39.7, 33.1, 21.2, 20.3, 20.2, 17.0.

4-((3-Cyanopropyl)sulfonyl)methyl-1H-tetrazol-1-yl)benzonitrile (3ax); yield: 16.7 mg (26%); pale yellow solid; m.p.: 138.0 - 139.6 °C. $^1$H NMR (400 MHz, Acetone-d$_6$) δ (ppm) 8.19 - 8.13 (m, 2H), 8.04 - 7.98 (m, 2H), 5.13 (s, 2H), 3.66 - 3.52 (m, 2H), 2.76 (t, $J$ = 7.2 Hz, 2H), 2.32 - 2.22 (m, 2H). $^{13}$C NMR (100 MHz, Acetone-d$_6$) δ (ppm) 147.0, 137.0, 134.1, 126.8, 118.6, 117.3, 114.7, 51.1, 47.1, 18.3, 15.36. HRMS (ESI) calcd for C$_{13}$H$_{13}$N$_5$O$_2$S$: 317.0815 (M+H$^+$), found: 317.0810.

4-((3-Cyanopropyl)sulfonyl)methyl-1H-tetrazol-5-yl)benzonitrile (3ax$^*$); yield: 7.3 mg (12%); white solid; m.p.: 151.4 - 152.6 °C. $^1$H NMR (400 MHz, DMSO-d$_6$) δ (ppm) 8.15 - 8.11 (m, 2H), 8.08 - 8.04 (m, 2H), 6.38 (s, 2H), 3.53 - 3.40 (m, 2H), 2.68 (t, $J$ = 7.2 Hz, 2H), 2.10 - 1.96 (m, 2H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ (ppm) 155.1, 133.6, 130.6, 127.8, 120.0, 118.5, 114.7, 63.4, 50.5, 17.8, 15.7. HRMS (ESI) calcd for C$_{13}$H$_{13}$N$_5$O$_2$S$: 317.0815 (M+H$^+$), found: 317.0806.
4. Data S2. The copies of NMR spectra, Related to Scheme 2, Scheme 3 and Scheme 4.
3ma
Acetone-d$_6$
5. Supplemental references
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