Combinatorial Synthesis of 3,5-Dimethylene Substituted 1,2,4-Triazoles

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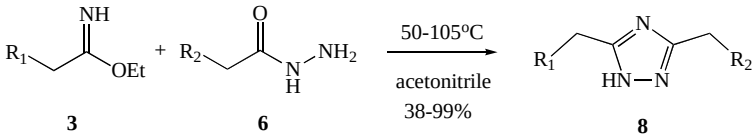
Abstract: Combinatorial cyclizations of imidates and hydrazides with methylene linked R groups, generated from the corresponding nitriles and carboxylic acids, respectively, provided a large library of 3,5-dimethylene substituted 1,2,4-trizoles.



3 **6** **8**

Keywords: Cyclizations, combinatorial chemistry, 1,2,4-triazoles, Pinner reaction, hydrazides, imidates.

Substituted 1,2,4-triazoles [1] have become very important in medicinal chemistry due to their ability to display a high degree of structural diversity around a rigid core, their ability to act as hydrogen bond donors or acceptors, and act as potent agonist or antagonist receptor ligands [2-5]. They have also been used as amide bond isosteres [6-8] in attempts to increase bioavailability of the parent bioactive molecules, and have been incorporated into peptides as *cis*-amide bond surrogates [9]. Although several different methods for the synthesis of 3,5-disubstituted 1,2,4-triazoles have been reported [10-19] for the purposes of this file enrichment library, we chose to condense imidates with hydrazides to form the desired triazoles [20-27], allowing for a large degree of functional group compatibility in the set.

A diverse set of imidates **3** was synthesized from their corresponding nitriles **1** (Fig. **1**), *via* the Pinner reaction [28-31], followed by neutralization of the resulting imidate HCl salt **2** with the trialkylamine ion exchange resin, Amberlyst A-21 (Scheme **1**). This resin was used in place of saturated K2CO3 solution to allow for a simple filtration work-up, so as to avoid losing water soluble imidate products during an aqueous work-up.

A diverse set of hydrazides **6** was then synthesized from their corresponding carboxylic acids **4** (Fig. **2**), *via* esterification **5** followed by reaction with hydrazine [32] (Scheme **2**).

In order to sample a different region of shape space in this library than what is achieved when R groups are directly attached to 5 and 6 membered rings, both the nitriles **1** and carboxylic acids **4** were chosen, in most cases, to include methylene groups between the functional group and the diversity element. This spacer allowed for increased side-chain flexibility and a wider variety of R groups to be tolerated in the library by minimizing the impact of the R group's electronic and steric factors on the core forming reaction. As a result, R groups such as the amino acids could be additionally elaborated to further increase the complexity of the molecules. The target triazoles could also be alkylated to obtain a third point of diversity.

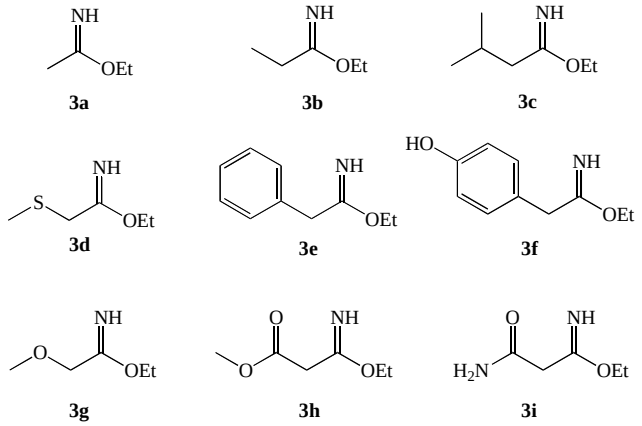
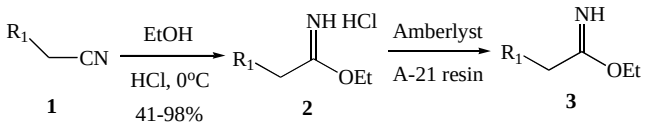
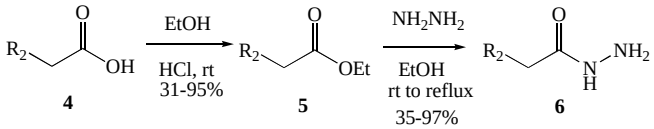


Fig. (1). Methylene substituted (R1) imidate **3** building blocks.



Scheme 1. Synthesis of methylene substituted imidates.



Scheme 2. Synthesis of methylene substituted hydrazides.

Once the imidates **3** and hydrazides **6** had been synthesized, they were thermally condensed in parallel sealed vials to first form an *in situ* acylamidrazone intermediate **7** at 50°C, followed by increased heating to 105°C to form the target triazole **8** (Scheme **3**). Attempts at

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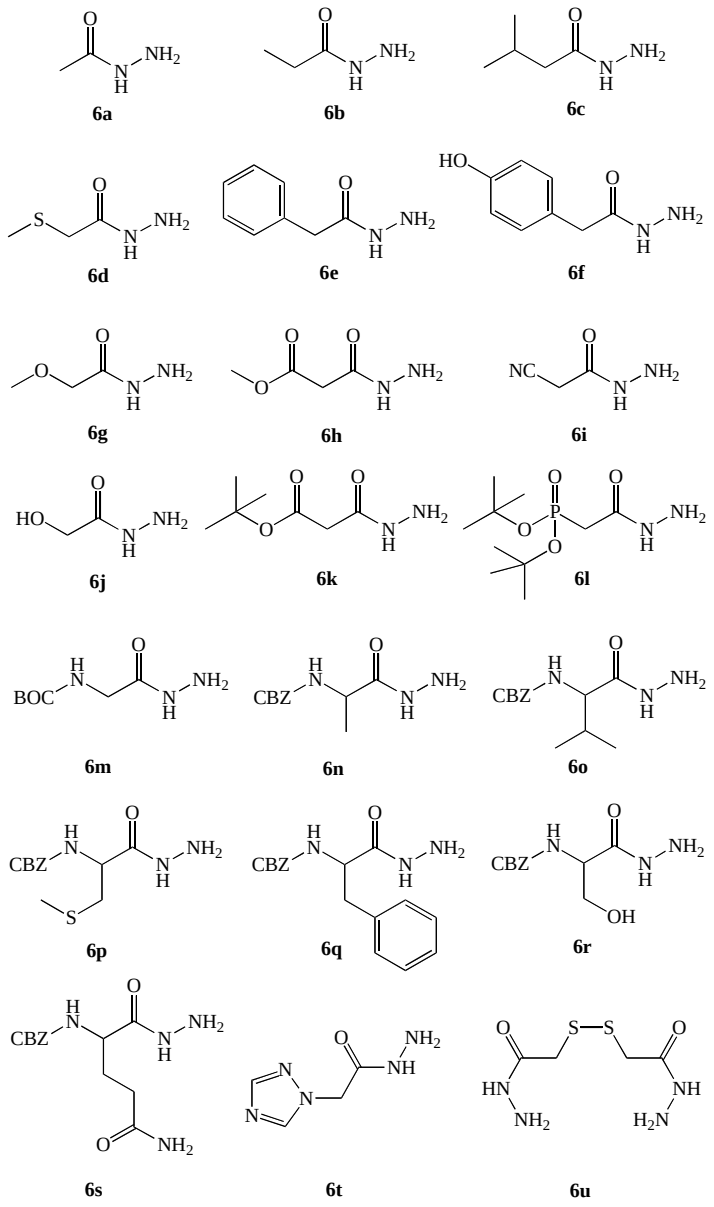
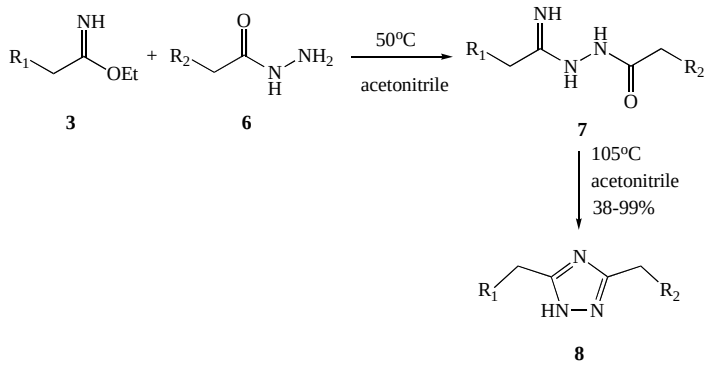


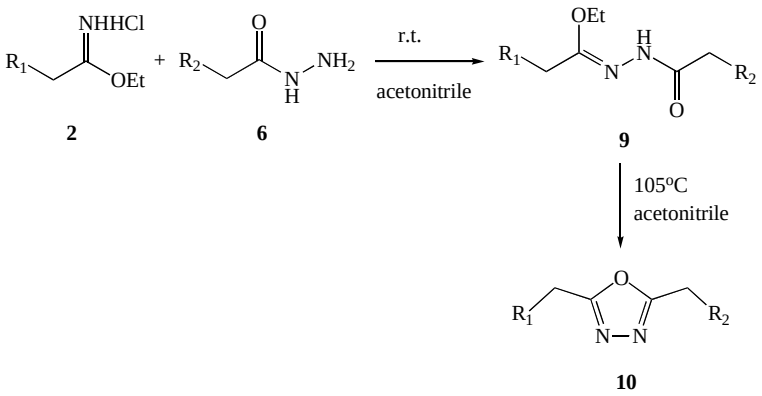
Fig. (2). Methylene substituted (R2) hydrazide building blocks.

simply heating to 105°C for the entire reaction resulted in decreased yields of the target triazole.

It was necessary to neutralize the imidate salts **2** before the condensation step to avoid undesired 1,3,5-oxadiazole **10** formation [33-35] (Scheme **4**).



Scheme 3. Synthesis of 3,5-dimethylene substituted 1,2,4-triazoles.



Scheme 4. Undesired Formation of 1,3,5-oxadiazoles from imidate HCl salts **2**.

The target triazoles **8** were labeled with the first letter corresponding to the R1 group from the imidate **3** and the second corresponding to the R2 group from the hydrazide **6** (i.e. – triazole **8ad** comes from imidate **3a** and hydrazide **6d**). In the cases where a product contained a protecting group, the de-protected product was labeled with an * (i.e.- triazole **8am** corresponds to the 3-methyl-5-BOC glycine analog, and triazole **8am*** corresponds to the de-protected 3-methyl-5-aminomethyl analog). From the 161 unique products synthesized, a representative selection of 3,5-dimethylene substituted 1,2,4-trizoles **8** are shown in Fig. (**3**). Product yields for successful reactions ranged from 38-99% after silica column purification, with an average yield being 75%.

In summary, several new 3,5-dimethylene substituted 1,2,4-triazoles were synthesized in a parallel fashion, from the corresponding nitriles and carboxylic acids, *via* a two stage heating process. This synthesis strategy allowed for the successful incorporation of a large, diverse set of functional groups into the target molecules that were available for further elaboration. Amberlyst A-21 resin proved to be very useful in neutralizing imidate HCl salts, in a non-aqueous environment.

EXPERIMENTAL

General Procedure A. Formation of Imidate hydrochlorides (2) from nitriles (1). A nitrile **1** (0.500 mol) and ethanol (29.9 ml, 0.510 mol) were added to a 100 ml round bottom flask under N_2 and cooled to 0°C. Anhydrous HCl gas (18.8 g, 0.515 mol) was introduced over 5 minutes. The flask was sealed and placed in a 0°C freezer where crystallization of the imidate HCl took place (1 to 10 days), forming a solid cake in the flask. The solid was broken up and washed with cold diethyl ether *via* vacuum filtration, then vacuum dried. All products were characterized by ^{1}H NMR. Representative compounds are shown below.

2a. Methyl imidate HCl. Used general procedure A to react acetonitrile with ethanol and HCl in 97% yield; ^{1}H NMR (300 MHz, d-DMSO) δ 1.35 (t, 3H, J=7.05 Hz), 2.37 (s, 3H), 4.40 (q, 2H, J=7.05 Hz), 11.05 (br s, 1H), 11.75 (br s, 1H).

2e. Benzyl imidate HCl. Used general procedure A to react benzylcyanide with ethanol and HCl in 92% yield; ^{1}H NMR (300 MHz, d-DMSO) δ 1.28 (t, 3H, J=7.05 Hz), 4.01 (s, 2H), 4.41 (q, 2H, J=7.05 Hz), 7.38 (m, 5H), 11.75 (br s, 2H).

General Procedure B. Formation of Imidates (3) from Imidate hydrochlorides (2). An imidate hydrochloride **2** (31.5 mmol) was added to a 100 ml round bottom flask, followed by Amberlyst A-21 resin (9.37 g, 48.4 mmol). 40 ml of dry acetonitrile was added and the flask was hand-swirled over 15 minutes. To test reaction completion, a very small amount of the solution was added to dilute nitric acid, followed by addition of AgNO3. After 5 minutes, the solution was checked to make sure no precipitates had formed. If not, the solution of the free imidate **3** was filtered away from the resin and the resin washed with acetonitrile. The solution was diluted to 200 ml for use in the parallel synthesis.

General Procedure C. Formation of Carboxylic esters (5) from carboxylic acids (4). Anhydrous HCl gas was introduced to the alcohol (methanol or ethanol) in a 500 ml flask. The carboxylic acid **4** was added and stirred at room temperature for 1-3 days. Reaction completion was checked periodically by NMR. After completion, the reaction mixture was evaporated and the resulting oil dissolved in ethyl acetate. The solution was then washed with a K_2CO_3 solution, dried over $MgSO_4$, evaporated and vacuum dried. All products were characterized by ^{1}H NMR. Representative compounds are shown below.

5m. N-Carbobenzoxyglycine ethyl ester. Used general procedure C to react carbobenzoxyglycine with ethanol in 91% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3H, J=7.55 Hz), 4.01 (m, 2H), 4.24 (q, 2H, J=7.65 Hz), 5.13 (s, 2H), 5.36 (br s, 1H), 7.40-7.43 (m, 5H).

5s. N-Carbobenzoxyglutamine methyl ester. Used general procedure C to react **3-U** with methanol in 72% yield; ^{1}H NMR (300 MHz, d-DMSO) δ 1.65-2.03 (m, 2H), 2.16 (m, 2H), 3.64 (s, 3H), 4.06 (m, 1H), 5.04 (s, 2H), 6.79 (br s, 2H), 7.36 (m, 5H), 7.77 (d, 1H, J=9.66 Hz).

General Procedure D. Formation of Hydrazides (6) from carboxylic esters (5). Anhydrous hydrazine was added to a solution of the ester **4** in ethanol at 0°C and the reaction allowed to warm to room temperature while stirring. In most cases, a white precipitate formed, causing the reaction mixture to solidify. A few reaction had to be refluxed before the precipitate formed. The precipitate was collected, washed with ether and vacuum dried. All products were

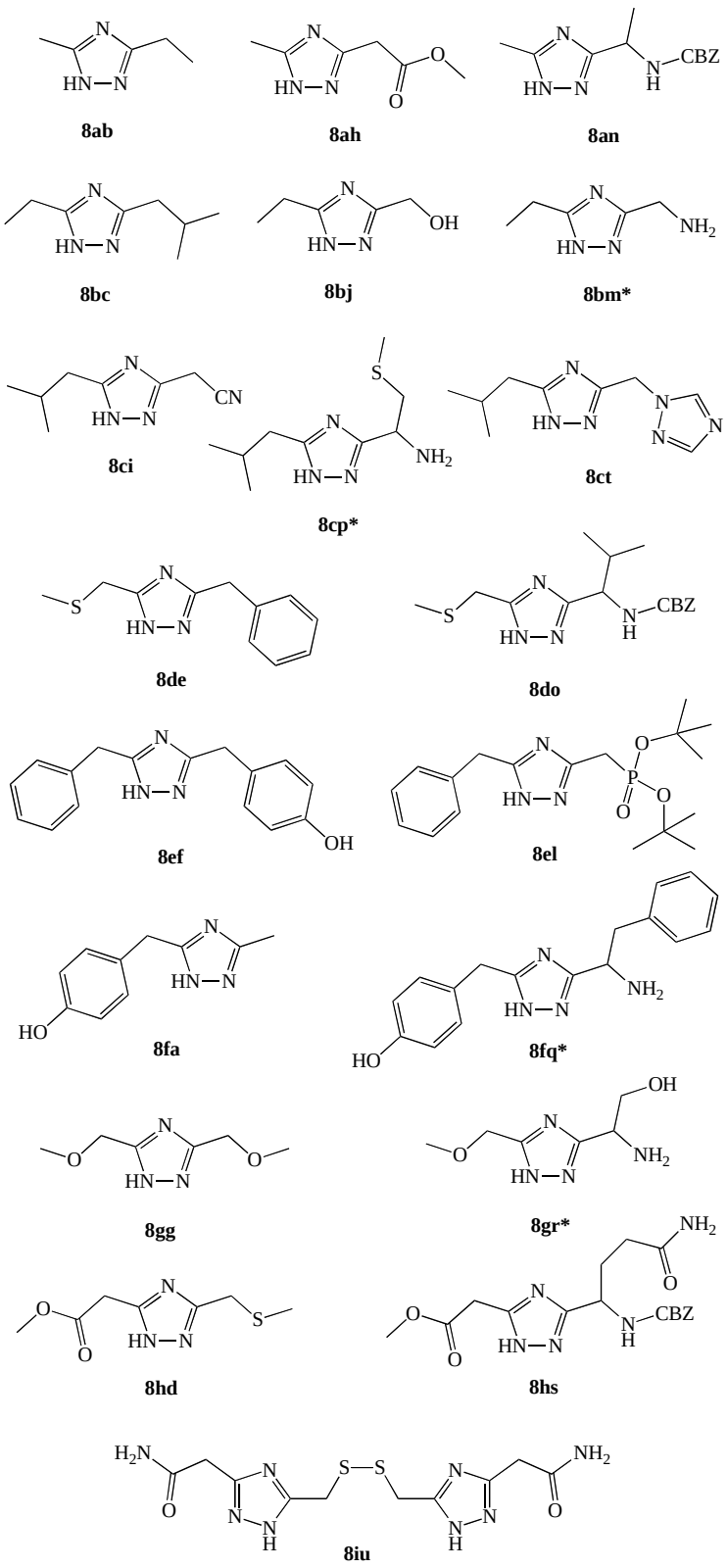


Fig. (3). 3,5-Dimethylene substituted 1,2,4-triazoles.

characterized by ^{1}H NMR. Representative compounds are shown below.

6c. Isovaleroic hydrazide. Used general procedure D to react ethyl isovalerate with hydrazine at reflux in 40% yield; ^{1}H NMR (300 MHz, d-DMSO) δ 0.86 (d, 6H, J=6.44 Hz), 1.89, (d, 2H, J=6.25 Hz), 1.94 (m, 1H), 4.17 (br s, 2H), 8.93 (br s, 1H).

6d. Ethyl(methylthio)acetic hydrazide. Used general procedure D to react ethyl(methylthio)acetate with hydrazine

at reflux in 80% yield; ^{1}H NMR (300 MHz, d-DMSO) δ 2.10 (s, 3H), 3.00 (s, 2H), 4.26 (br s, 2H), 9.07 (br s, 1H).

General Procedure E. Formation of 3,5-dimethylene 1,2,4-triazoles (8) from Imidates (3) and hydrazides (6). A solution of free imidate **3** (1.5 mmol) in 9.5 ml acetonitrile was added to a vial containing a hydrazide **6** (1.5 mmol). The resulting solution was stirred and heated in a sealed vial to 50°C in a Pierce reactor overnight. The reaction was then heated to 105°C for an additional 24 hours, except for any reaction containing hydrazide **6l**, to which 5 ml of Hunig's base and excess K_2CO_3 was added and heated for 6 hours. The reaction was cooled and evaporated. A silica column was done to afford pure dimethylene triazole **8**. All products were fully characterized by GCMS and ^{1}H NMR. Representative compounds are shown below.

8ab. 3-Methyl-5-ethyl-1H-1,2,4-triazole. Used general procedure E to react imidate **3a** with hydrazide **6b** in 71% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (t, 3H, J=7.55 Hz), 2.48 (s, 3H), 2.81 (q, 2H, J=7.65 Hz), 6.83 (br s, 1H). GCMS 3.14 min, *m/z* 111, calcd. 111.17.

8ah. 3-Methyl-5-carbomethoxymethyl-1H-1,2,4-triazole. Used general procedure E to react imidate **3a** with hydrazide **6h** 84% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54 (s, 3H), 3.80 (s, 3H), 3.94 (s, 2H), 4.31 (br s, 1H). GCMS 4.76 min, *m/z* 155, calcd. 155.16.

8bj. 3-Ethyl-5-hydroxymethyl-1H-1,2,4-triazole. Used general procedure E to react imidate **3b** with hydrazide **6j** in 82% yield; ^{1}H NMR (300 MHz, d-DMSO) δ 1.37 (t, 3H, J=7.55 Hz), 2.83 (q, 2H, J=7.65 Hz), 4.81 (s, 2H). GCMS 5.59 min, *m/z* 127, calcd. 127.15.

8bm*. 3-Ethyl-5-aminomethyl-1H-1,2,4-triazole. Used general procedure E to react imidate **3b** with hydrazide **6m,** followed by deprotection of the BOC with TFA in 75% overall yield; ^{1}H NMR (300 MHz, d-DMSO) δ 1.24 (t, 3H, J=7.55 Hz), 2.74 (q, 2H, J=7.65 Hz), 4.04 (m, 2H), 8.38 (br s, 2H).

8ci. 3-Isovaleryl-5-cyanomethyl-1H-1,2,4-triazole. Used general procedure E to react imidate **3c** with hydrazide **6i** in 80% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (d, 6H, J=6.65 Hz), 2.16 (m, 1H), 2.72 (d, 2H, J=7.25 Hz), 3.92 (s, 2H). GCMS 6.26 min, *m/z* 164, calcd. 164.20.

8ct. 3-Isovaleryl-5-(N-methylene-1,2,4-triazole)-1H-1,2,4-triazole. Used general procedure E to react imidate **3c** with hydrazide **6t** in 81% yield; ^{1}H NMR (300 MHz, d-DMSO) δ 0.87 (d, 6H, J=6.65 Hz), 1.95 (m, 1H), 2.51 (d, 2H, J=7.25 Hz), 5.40 (s, 2H), 7.95 (s, 1H), 8.58 (s, 1H). GCMS 7.78 min, *m/z* 206, calcd. 206.25.

8de. 3-(Methylthio)methyl-5-benzyl-1H-1,2,4-triazole. Used general procedure E to react imidate **3d** with hydrazide **6e** in 69% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3H), 3.78 (s, 2H), 4.15 (s, 2H), 7.32 (m, 5H). GCMS 8.46 min, *m/z* 219, calcd. 219.30.

8el. 3-Benzyl-5-(di-t-butyl phosphonomethyl)-1H-1,2,4-triazole. Used general procedure E to react imidate **3e** with hydrazide **6l** in 51% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 18H), 3.28 (d, 2H, J=20.75 Hz), 4.09 (s, 2H), 7.31 (m, 5H). ^{19}F NMR (d-DMSO) δ14.55 (s).

8fa. 3-(4-Hydroxybenzyl)-5-methyl-1H-1,2,4-triazole. Used general procedure E to react imidate **3f** with hydrazide **6a** in quantitative yield; ^{1}H NMR (300 MHz, d-DMSO) δ 2.19, 2.25 (s, 3H), 3.72, 3.84 (s, 2H), 6.67 (m, 2H), 7.05 (d, 2H, J=8.25 Hz), 9.14, 9.25 (s, 1H). GCMS 8.85 min, *m/z* 189, calcd. 189.27.

8gg. 3,5-Dimethoxymethyl-1H-1,2,4-triazole. Used general procedure E to react imidate **3g** with hydrazide **6g** in 66% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.52 (s, 6H), 4.65 (s, 4H). GCMS 4.94 min, *m/z* 156, calcd. 157.18.

8hs. 3-Carbomethoxymethyl-5-(1-(N-benzylcarboxyl-amino)-3-carboxamide-propyl)-1H-1,2,4-triazole. Used general procedure E to react imidate **3h** with hydrazide **6s** in 95% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (m, 2H), 3.79 (s, 3H), 3.89 (m, 2H), 3.91 (m, 2H), 5.02 (m, 1H), 5.09 (s, 2H), 5.51 (m, 2H), 6.05 (m, 1H), 7.35 (m, 5H).

8iu. Bis(3-acetamide-5-thiomethyl-1H-1,2,4-triazole). Used general procedure E to react imidate **3i** with hydrazide **6u** in 38% yield; ^{1}H NMR (300 MHz, d-DMSO) δ 3.38 (s, 4H), 3.92 (s, 4H), 7.15, 7.56 (br s, 4H).

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