Full Paper

Preparation of 2-(2H-Tetrazol-2-yl)benzoic Acids via Regioselective Cu(I) Catalyzed N2 Arylation of Tetrazole

Zhiguo Jake Song, Peter E. Maligres, Carmela Molinaro, Guy R. Humphrey, Jeff Fritzen, Jonathan Wilson, and Yonggang Chen

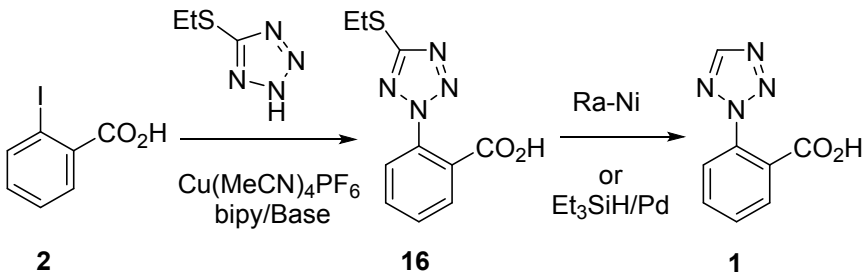
Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.9b00243 • Publication Date (Web): 30 Sep 2019

Preparation of 2-(2*H*-Tetrazol-2-yl)benzoic Acids via Regioselective Cu(I) Catalyzed N2 Arylation of Tetrazole

Zhiguo Jake Song, Peter Maligres*, Carmela Molinaro, Guy Humphrey, Jeff Fritzen, Jonathan Wilson, Yonggang Chen.*

Process Research & Development, Merck & Co. Inc, P.O. Box 2000, Rahway, NJ 07065, USA.

Scheme for TOC

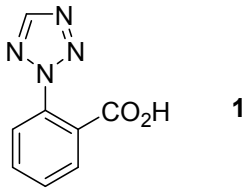


ABSTRACT 2-(2*H*-Tetrazol-2-yl)benzoic acid **1** and analogs were prepared via Cu(I) catalyzed C-N coupling of 2-iodo or 2-bromo benzoic acids with 5-(ethylthio)-1*H*- tetrazole followed by reductive cleavage of the thioether bond. The C-N coupling was regioselective toward the N2-position on tetrazole. The scope of this methodology was demonstrated on a series of 2-halobenzoic acid substrates in moderate yields.

KEYWORDS: Tetrazole benzoic acid, *N-2* regioselective tetrazole arylation,

Introduction

Tetrazoles are important building blocks in organic synthesis. They play important roles in materials, catalysis and biologically active compounds.[1] Tetrazole structures have been found in several important drugs.[2] Depending on the substitution patterns on the tetrazoles, their preparative methods, especially on scale, range from relatively well established to rather specific. While 5-substituted (C-substituted) tetrazoles are readily accessible from nitrile compounds and azides, 1-(N1-) and 2-(N2-) substituted tetrazoles are much less accessible.[3] In this paper, we report the development of a scalable method for preparing N2 arylated tetrazole **1** (Figure 1) and analogs.



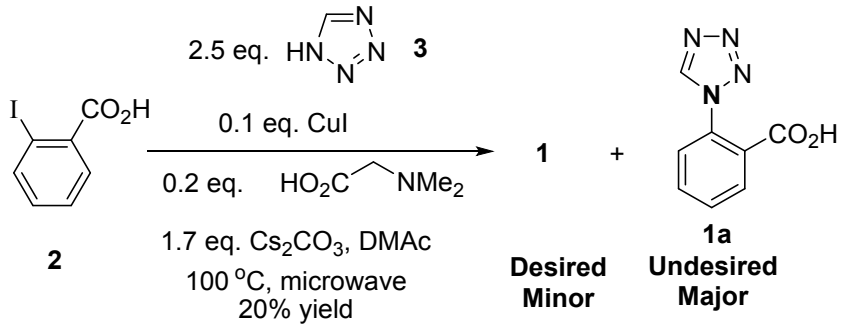
1

Figure 1: 2-(2*H*-Tetrazol-2-yl)benzoic Acid

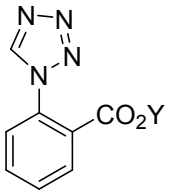
Results and Discussion

Arylation of Tetrazole The prior route to the substituted tetrazole **1** involved an Ullman type[4] copper (I) catalyzed, microwave-promoted *N*-arylation of tetrazole **3** with 2-iodobenzoic acid (**2**) in DMAc at 100 °C. Unfortunately, this reaction gave a mixture of the two regio isomers **1** and **1a** in 1:4 ratio, favoring the undesired isomer. The isolated yield of **1** after chromatography was ca. 20% (Scheme 1).[5]

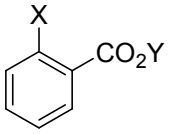
Scheme 1: Direct Arylation of Tetrazole



In an attempt to improve the yield of this reaction, high throughput screening of the reaction variables including Cu and Pd catalysts, bases, solvents and aryl substrates **2, 2a, 4, 5** (aryl iodide, fluoride, boronic acid) was carried out. Most reactions gave no product or proceeded with very low conversions. In all cases, where products were formed, the major isomer was the undesired N1 substituted tetrazole product **1a** or **1b** (Figure 2).



1a (Y = H)
1b (Y= Me)



2 (X = I, Y = H)
2a (X = I, Y = Me)
4 (X = F, Y = Me)
5 (X = $B(OH)_2$, Y = Me)

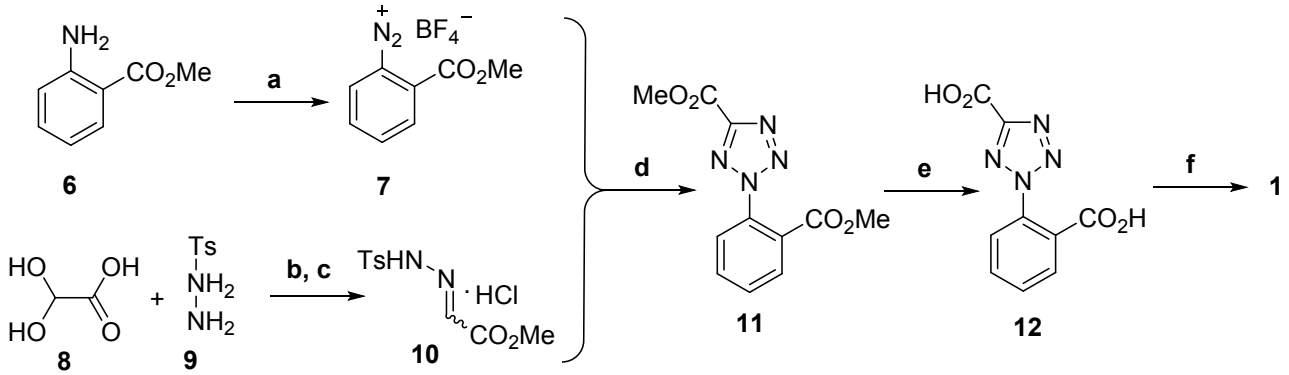
Figure 2

Although this approach did provide a few hundred milligrams of material to support the initial SAR efforts, this route was not scalable due to low yield and poor selectivity. Furthermore, handling of tetrazole poses serious safety challenges. We found that unsubstituted tetrazole **3** has an energy release of 1000 cal/g as determined by DSC with an initial decomposition temperature of 165 °C , and is difficult to obtain on scale. It is presumed to be shock sensitive and spontaneously decomposes with nitrogen gas release well below 100 °C in reaction mixtures. Therefore, a more practical synthesis of **1** was required.

The [3+2] Cycloaddition Approach: A *de novo* route to the tetrazole system was devised to set the desired regiochemistry. This approach (Scheme 2) is based on Kakehi's synthesis of 5-phenyltetrazole.[6] Thus, 2-(methoxycarbonyl)

benzenediazonium tetrafluoroborate salt (**7**) was prepared in quantitative yield from aniline **6** using non-aqueous conditions described by Doyle[6d] and isolated as a white powder. Compound **7** was tested and determined to be safe to prepare on >100g scale. Hydrazone formation using glyoxylic acid mono hydrate (**8**) and *p*-tosyl hydrazide (**9**) under acidic conditions followed by an esterification with TMS-Cl in MeOH provided an E/Z mixture of methyl 2-(2-tosylhydrazono)acetate (**10**) as a white solid in 61% overall yield.

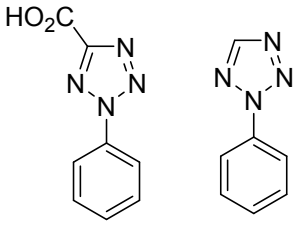
Scheme 2: [3+2] Cycloaddition Followed by Decarboxylation



(a) 1.5 eq. BF_3OEt_2, 1.2 eq. t-butyl nitrite, DCM, hept, quant ; (b) 1.2 eq. HCl, water, 55 ^oC, 81% (c) 2 eq. TMS-Cl, MeOH, r.t., 75 ^oC, 75% (d) 2 eq. TEA/ACN, ***slow addition,*** ACN, -10-0 ^oC. (e) 1). Darco KB-G, THF 2). 2.5 eq. 19M NaOH, EtOH, r.t. 75% for 2 steps. (f) 4 eq. aq H_2SO_4, DMSO, 124 ^oC, 70%.

For the key [3+2] cycloaddition step,[7] we found that slow addition of 2 eq. of triethylamine[7c] to the mixture of **7** and **10** at -10 °C in acetonitrile resulted in clean formation of tetrazole diester **11,** none of the N1 substituted tetrazole was observed. A

Darco KB-G treatment at this stage followed by saponification provided diacid **12** in 75% yield for the two steps. Thermal decarboxylation of **12** provided the desired product **1**, undesired isomer **13** and 2-phenyl-2H-tetrazole **14**.[6g] A screen of acids, bases and polar/water miscible solvents was carried out for this step and H_2SO_4 in DMSO/water mixture was identified to provide the best overall performance. With 4 eq. H_2SO_4 in DMSO in the absence of water at 124 °C, the reaction gave 70% isolated yield of desired compound **1** on 90g scale. But it was also observed that the assay yield reached a maximum at ~8 hours and dropped drastically with longer reaction time (e.g., assay yield was 80% at 8 hours but 55% at 25 hours).



13 **14**

Figure 3

The [3+2] cycloaddition route employs readily available starting materials and generated the desired N2- regio isomer. However, the long cumbersome sequence and

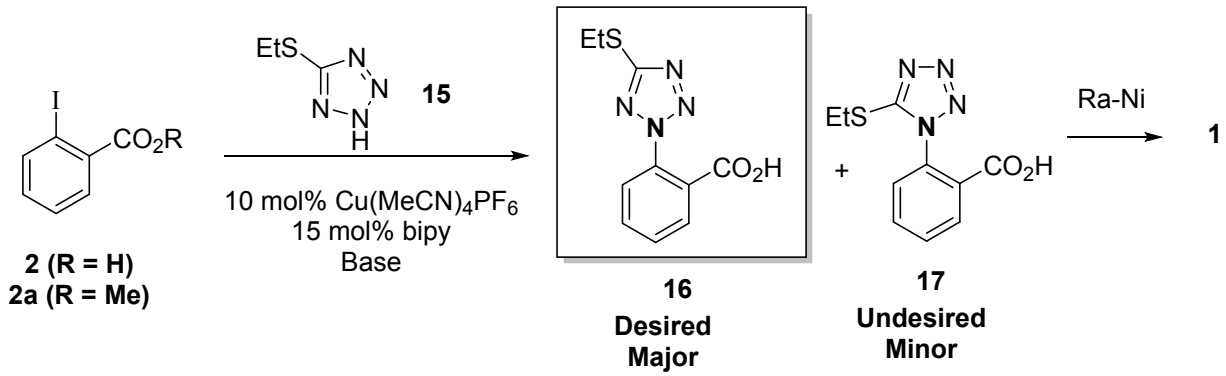
high energy intermediates in this route prompted us to explore more practical alternatives for larger scale deliveries.

Arylation of Ethylthiotetrazole. For kilogram quantity preparations, we re-evaluated the N-arylation of tetrazole. N2 selective arylations of 5-substituted tetrazoles have been reported with very reactive diaryliodonium salts under the catalysis of Cu(I) salt or palladium catalysts.[8a,b] It is also known that aryl boronic acids can undergo oxidative C-N coupling with 5-substituted tetrazoles catalyzed by copper salts.[8c,d] Although S_NAr type displacement of activated aryl fluorides with 5-substituted tetrazoles is known, the scope is very limited and the regio selectivities were poor [9] We reasoned that the low yield of direct C-N coupling with tetrazole itself was the result of its low thermal stability and weak nucleophilicity. Employing a 5-substituted tetrazole was expected to increase both the thermal stability and the nucleophilicity. While a variety of 5-substituted tetrazoles such as 5-methyl, 5-methylthio, 5-phenyl-, 5-ethylthio and 5-benzylthio-1*H*-tetrazole are commercially available, only 5-ethylthio-1*H*-tetrazole (**15**) is readily available, inexpensive, and stable with low molecular weight. Additionally, conditions are known to cleave the alkylthio ether bonds on aromatic rings with Raney-

Ni or Pd catalysts; therefore, we decided to focus our efforts on this reagent for the N2 arylation.[10]

High throughput screening of the reaction between 5-ethylthio-1*H*-tetrazole (**15**) and methyl 2-iodobenzoate (**2a**), in the presence of $Cu(MeCN)_4PF_6$, was carried out with 22 ligands and three carbonate bases (K_2CO_3, Na_2CO_3, Cs_2CO_3) in DMAc solvent at 120 °C.[11] In most cases a 9:1 mixture of desired N2 and undesired N1 regio isomers of the carboxylic acids **16** and **17** were observed, albeit in low yields.[12] Using 2,2'-bipyridine as ligand, K_2CO_3 as base, the desired isomer acid **16** was obtained in 30% HPLC assay yield.

Scheme 3. N2-Arylation of 5-Ethylthiotetrazole (15)



In comparison, the C-N coupling of 5-ethylthio-1*H*-tetrazole (**15**) and 2-iodobenzoic acid (**2**) was also screened under the similar conditions and found to be much more facile and higher yielding.[13] The formation of only the carboxylic acid product in the original screen was likely because the ester was partially hydrolyzed before undergoing C-N coupling. The same 2,2'-bipyridine in combination with the soluble $Cu(MeCN)_4PF_6$ was found to be the optimal catalyst. Potassium phosphate was found to be the best base among the weak bases sceened.[14] Reaction temperature was also optimized and 85 °C was found to be better than the original 120 °C. A by-product observed during this screen was the formation of salicylic acid due to the C-O coupling of adventitious moisture present in K_3PO_4 with aryliodide **2.** After further exploration it was found that the use of excess 2-ethylthiotetrazole (**15**) (2 equivalents) reduced the formation of salicylic acid. An initial solvent screen showed the general trend observed was that the reaction gave better conversion and yields in polar ether type solvents such as 1,4-dioxane and DME. In order to rapidly deliver bulk material for subsequent studies dioxane was chosen as the solvent for further scale up. Subsequently, a more comprehensive solvent screen was conducted to avoid the use of the toxic 1,4-

dioxane.[15] The general trend observed was the same as before, better results were obtained in polar ether type as well as in nitrile solvents such as 1,4-dioxane, 1,3-dioxolane, DME, acetonitrile, benzonitrile, tetrahydropyran, and *N*-methylmorpholine. The three most promising hits were scaled up on 5 mmol scale and the results are shown on Table 1.

Table 1 : N-Arylation in the Best Solvents[a]

Entry	Solvent	Ratio[c] **16 : 17**	Assay Yield **16** (%)	Isolated Yield[d] **16** (%)
1	MeCN	6.7 : 1	69	61
2	Dioxolane	8.7 : 1	78	66
3[b]	Dioxane	10.8 : 1	81	66

[a]Reaction conditions: 10 mol% $Cu(MeCN)_4PF_6$, 15 mol% bipy, 3 eq. K_3PO_4, solvent, 85 °C, 18 h on 5 mmol scale except entry 3. [b]20 mol run. [c]At the end of reaction. [d]After washing cake with water, desired isomer only.

Work-up of this reaction presented some challenges. Precipitation of insoluble, difficult to filter copper salts was observed when aqueous acid was added to the reaction mixture to convert the carboxylate salt to the organic soluble free acid. This

challenge was addressed by adding zinc dust to the mixture to reduce the copper species to copper metal, which was easily filtered off from the reaction mixture. After extraction with cyclopentylmethyl ether (CPME), the coupling product **16** was isolated as the diisopropylamine salt in 66% isolated yield with 94% LC purity (6% of isomer **17,** yield corrected for purity).

The removal of the ethylthio group was screened under oxidative (H_2O_2/HOAc, NaOCl/aq THF, $NaNO_2$/HOAc) and reductive (hydrogenolysis in the presence of metal catalysts, $Et_3SiH/PdCl_2$/TMSCl, Et_3SiH/Pd-C) conditions. The oxidative reactions gave complex reaction mixtures. The palladium catalyzed triethylsilane reduction gave desired product but produced ethanethiol (stench). A screen of reductive cleavage under hydrogenation conditions catalyzed by several commercially available Raney nickel and palladium catalysts identified inexpensive Raney Nickel A-5B09 as a convienent reagent.[10] It was found that the Raney Nickel reduction could be performed at 50-70 °C in water as solvent without hydrogen, which alleviate the safety concerns related to filtration of the nickel in the presence of flammable solvents. The ethylthio group was cleaved to generate ethane gas and the sulfur was bound to the nickel as an

insoluble sulfide[17]. As a result, no appreciable stench was produced for this step. After Raney Nickel removal by filtration, the product was extracted with EtOAc under acidic conditions. The EtOAc extract was solvent switched to toluene from which **1** was crystallized in 80% yield and 99.9% purity with complete rejection of the undesired regioisomer. The structure of **1** was confirmed by NMR and by single crystal X-ray crystallography (Figure 3).[16]

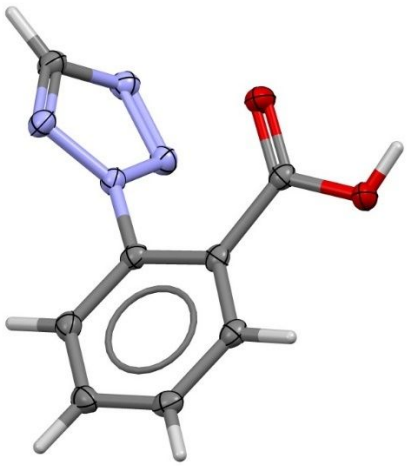
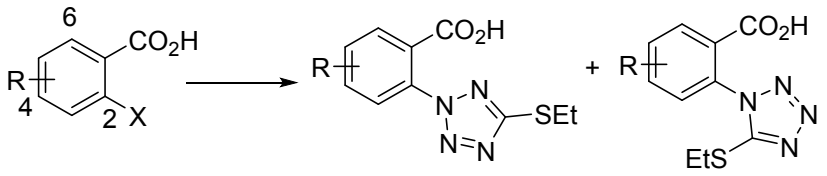


Figure 3 : X-Ray Structure Thermal Ellipsoid Representation of 1, with Thermal Ellipsoids Set at the 50% Probability Level.

Scope of Methodology: Given the success of the synthesis of **1** on kilogram scale, we evaluated the scope of this methodology. A series of 2-halo benzoic acid analogs were subjected to the C-N coupling reaction with 5-ethylthio-1*H*-tetrazole. Table 2 shows the substrates that gave useful yields of the desired N2 products. In general, bromo and iodo substrates performed similarly in these reactions. Other substituents had significant effects on the reactivities, e.g., the best performing substrates had electron donating groups such as methoxy or methyl *para* to the halogens (Table 2, entries 3 and 11). A nitro group *para* to the halogen resulted in lower yields (Table 2, entry 12). One interesting substrate is 2-bromo-6-iodo benzoic acid where the 6-iodo product was isolated (Table 2, entry 7). Even though it appears that the bromide reacted more readily than the iodide, a more likely explanation is that the iodide reacted first but the bromide product underwent halogen exchange to give the iodide product as the major product. Figure 4 shows the substrates that gave either messy profile or poor conversions. We also evaluated a number of other directing groups such as trifluoroacetamido, benzoimidazole. But none of them proved to be effective. The

presence of pyridine in the substrate lead to failed reactions in all cases, presumably caused by competing coordination of the basic nitrogen with Cu (I) catalyst.



substrates 18-29

N2 isomer **products 16, 30-38**

N1 isomer **products 17, 30a-38a**

Table 2: C-N Coupling of 5-Ethylthiotetrazole with 2-Halobenzoic Acids

entry	Substrate	Substrate X-	R-	Product N2/N1 isomer	Isomer ratio N2/N1	Isolated N2 isomer yield %
1	18	Br	H	16/17	3.7	56
2	19	Cl	H	16/17	7.2	31
3	20	Br	5-methoxy	30/30a	3.8	66
4	21	Br	5-bromo	31/31a	5.4	55
5	22	Br	4,5-difluoro	32/32a	10	54
6	23	Br	5-nitro	33/33a	-	20
7	24	Br	6-iodo	34/34a	-	26
8	25	I	4-bromo	35/35a	8.4	44
9	26	I	5-chloro	36/36a	27	54
10	27	I	5-fluoro	37/37a	6.9	62
11	28	I	5-methyl	38/38a	5.7	73
12	29	I	5-nitro	33/33a	-	22

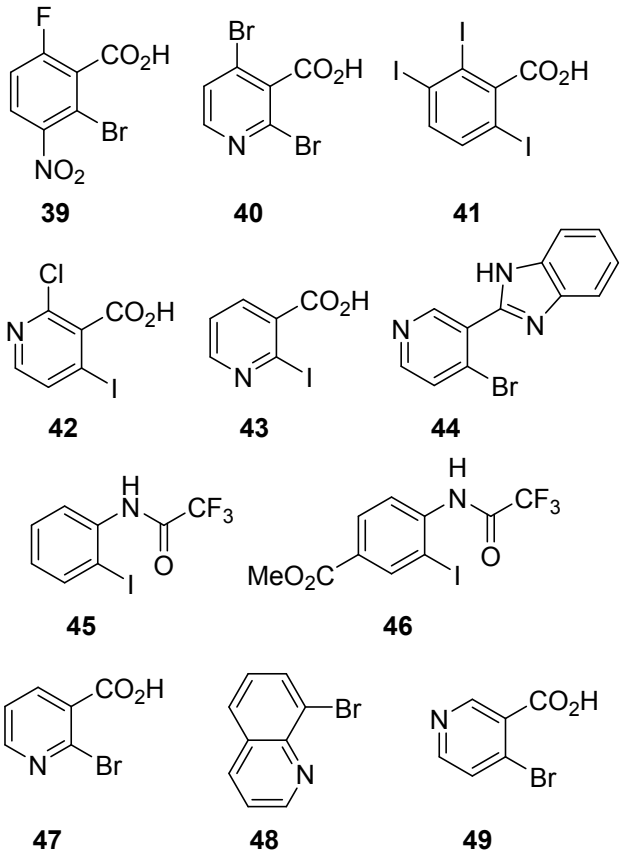
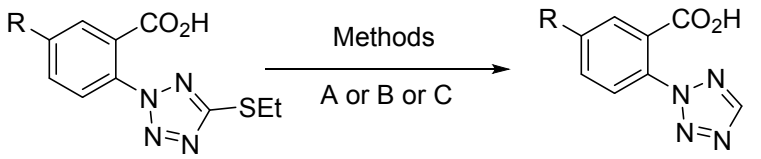


Figure 4: Poor Substrates

Three of the C-N coupling products were subjected to reductive cleavage conditions to remove the ethylthio group. In addition to the Raney nickel conditions, palladium catalyzed reduction with triethylsilane was also demonstrated to be effective. Both methods were applied to each of the 3 compounds **36**, **37, 38**, and the yields are listed in Scheme 4. For reduction with triethylsilane, relatively high palladium loading (method B) appeared to be needed for complete conversion and high yield. This is

recommended for small scale reactions. Raney nickel maybe cost effective on larger scale, but in case of compound **36**, significant amount of compound **16** was formed as side product in the Raney reduction step.

Scheme 4



	Methods/Yields A (IY)	B (AY)	C (AY)	
36: R = Cl	76%	91%	42%	**50**: R = Cl
37: R = F	39%	88%	75%	**51**: R = F
38: R = Me	49%	87%	53%	**52**: R = Me

Methods: (A) Et_3SiH/10% Pd/C (10%wt loading)
(B) Et_3SiH/10% Pd/C (100%wt loading)
(C) Ra Ni
IY = Isolated Yield, AY = Assay Yield

In summary, scalable regioselective N2 arylation of tetrazole was achieved by copper (I) catalyzed C-N coupling of 2-iodo and 2-bromo benzoic acid with 5-ethylthio-1*H*-tetrazole followed by thioether cleavage. This methodology was applied to several analogs and compound **1** was scaled up to kilogram scale.

Experimental Section.

General Reagents and solvents were purchased from commercial suppliers and used as received unless otherwise noted. Reaction conversion and assay yields were calibrated against isolated pure standards by HPLC. Compound characterizations were carried out on samples purified via standard silica gel columns and confirmed to be 95% or higher purity by HPLC.

2-(5-(Ethylthio)-2H-tetrazol-2-yl)benzoic acid from 2-iodobenzoic acid (16). To a 100-L 3-neck glass vessel equipped with a mechanical stirrer, nitrogen inlet and thermocouple probe under nitrogen atmosphere, 5-(ethylthio)-1*H*-tetrazole **15** (5.21 kg, 40.0 mol), 2-iodobenzoic acid **2** (4.96 kg, 20 mol), 2,2'-bipyridine (0.469 kg, 3.00 mol), tetrakis(acetonitrile) copper(I) hexafluorophosphate (0.745 kg, 2.000 mol), potassium phosphate (12.74 kg, 60.0 mol) and 1,4-dioxane (24.80 L) were added. The dark red mixture was heated to 86-88 °C for 14 h. HPLC analysis after 14 h indicated product (**16**) /isomer (**17**) /iodobenzoic acid (**2**) = 88.6/11.4/0.0. The mixture was cooled to 42 °C; then zinc dust (0.497 kg, 7.60 mol), 5M aq HCl (24 L, 120 mol, pre-cooled to 5 °C), and water (9.92 L) were added sequentially maintaining the temperature below 63 °C.

Solka-Floc (500 g), Darco KB charcoal (0.500 kg, 41.6 mol) and CPME (12.40 L) were added. The mixture was stirred for 45 min and filtered through Solka-Floc pad. The filter cake was washed with CPME (37.2 L). The combined filtrate was transferred to a 100-L extractor through an inline filter and heated to 40 °C. The phases were separated, and the organic phase was washed with water (2 x 9.92 L). HPLC analysis of the final organic phase indicated 6.23 kg, 88.6% assay yield of **16** and **17** (**16**/**17** = 91.5/8.5). The organic phase was concentrated to 37 L volume under vacuum (70-80 °C batch temperature). Diisopropylamine (6.27 L, 44.0 mol) was added to the homogeneous mixture over 30 min with stirring at 76-90 °C to give a tan slurry. The slurry was cooled to 25 °C over 1 h and aged for an additional 1 h. The crystalline solid was collected by filtration and washed with CPME (25 L). The filter-cake was slurry washed with water twice (5 Lx2) to remove residue tetrazole **15**. The off-white solid was dried on the filter pot under nitrogen stream to give diisopropylamine salt of **16** (5.22 kg, 13.9 mol total,**16/17** = 93.91/6.09 with <0.3A% **15,** 66.4 % yield for **16**). A small sample of the isolated solid diisopropylamine salt was converted to the free acid by partitioning between 1M aq HCl and MTBE followed by separation of the isomers by preparative

TLC (silica gel, MTBE); Major isomer: ^{1}H-NMR (500 MHz, CD_3CN): δ 1.45 (t, *J* = 7.3 Hz, 3H), 3.29 (q, *J* = 7.3 Hz, 2H) , 7.77 (m, 2H), 7.84 (m, 1H), 8.05 (m, 1H). ^{13}C-NMR (125 MHz, CD_3CN): δ 14.4, 26.5, 126.3, 127.4, 131.0, 131.2, 133.1, 135.3, 164.2, 165.3. . Minor isomer: ^{1}H-NMR (500 MHz, CD_3CN): δ 1.42 (t, *J* = 7.3 Hz, 3H), 3.30 (q, *J* = 7.3 Hz, 2H), 7.57 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.80 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.88 (dd, *J* = 7.7, 1.6 Hz, 1H), 8.05 (dd, *J* = 7.7, 1.6 Hz, 1H). ^{13}C-NMR (125 MHz, CD_3CN): δ 14.2, 27.5, 127.5, 128.5, 131.7, 132.1, 132.6, 134.0, 155.8, 164.3..

2-(2H-Tetrazol-2-yl)benzoic acid (1). To a 100-L glass vessel protected under nitrogen, equipped with a mechanical stirrer, nitrogen inlet/outlet and thermocouple probe, Raney nickel A-5B09 (Johnson-Matthey, ~19 kg Ni, ~330 mol, water slurry as supplied), water (4 L) and diisopropylamine salt of **16** (4.00 kg, 11.4 mol, 94/6 isomer mixture from previous step) were added. The mixture gradually evolved gas (believed to be ethane)[17] which was swept out with nitrogen flow. The mixture was heated to 50 °C, stirred at 50 °C for 2 h then 60 °C for 4 h. The mixture was cooled to room temperature and filtered through a Solka-Floc pad. The filter cake was washed with water (20 L, Caution: Cake

must be kept water wet throughout the filtration). The filtrate was mixed with sodium chloride (6 kg) and then 37% aq HCl (0.935 L, 11.38 mol), extracted twice with ethyl acetate (8 Lx2) at 35-40 °C. The combined organic phase was washed with brine (25% NaCl, 2 L) and dried over magnesium sulfate. After removal of magnesium sulfate by filtration, the solution was concentrated under vacuum and solvent switched to toluene by distillation with a final volume 24 L (<60 °C at 28" Hg vacuum). The mixture was heated to 91 °C to give a homogeneous solution, cooled to 87 °C and seeded with **1** (5 g). The mixture was gradually cooled to 22 °C over 2h. The solid was collected by filtration and the filter cake was washed with toluene (8 L), and dried under nitrogen stream to give 1.732 kg of **1** (83% yield). HPLC analysis indicated the crystalline solid product contained <0.05A% isomer **1a**. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.78-7.87 (m, 3H), 8.01 (m, 1H), 9.24 (s, 1H), 13.42 (br s, 1H) ; ^{13}C-NMR (100 MHz, DMSO-d_6): δ 126.9, 129.0, 131.1, 132.8, 134.2, 135.3, 154.0, 166.3..

General procedure for other analogs: A typical procedure is for the preparation of 2-(5-(ethylthio)-2H-tetrazol-2-yl)benzoic acid (16) from 2-bromobenzoic acid (18) To a 25

mL 2-neck flask were charged with 2-bromobenzoic acid **18** (200 mg, 1.0 mmol), 5-(ethylthio)-1*H*-tetrazole **15** (260 mg, 1.99 mmol), 2,2'-bipyridine (23.4 mg, 0.15 mmol), tetrakis(acetonitrile) copper(I) hexafluorophosphate (37.1 mg, 0.1 mmol), potassium phosphate (0.63 g, 2.98 mmol) and degassed 1,4-dioxane (2 mL). The mixture was heated to 86-88 °C overnight and cooled to room temperature. LCMS analysis showed desired product **16**/isomer **17**/**18** = 78.6/21.4/0.0. The mixture was poured into 50 mL water. The mixture was neutralized with AcOH to pH = 5 and extracted with EtOAc (50 mL x 3). The organic phase was concentrated and purified by Combi-Flash (ACN:H_2O with 0.05% TFA 30%-60%, 30min). 140 mg 2-(5-(ethylthio)-2H-tetrazol-2-yl)benzoic acid **16** (56%) was obtained as white solid. The assay yield was 69% which was determined by HPLC using a purified sample as standard. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.43 (t, J = 7.3 Hz, 3H), 3.24 (q, J = 7.3 Hz, 2H), 7.64–7.80 (m, 3H), 8.08 (d, J = 7.5 Hz, 1H), 11.60 (br s, 1H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 14.83, 26.73, 126.27, 126.32, 130.83, 131.63, 133.43, 135.78, 164.79, 169.77. HRMS (ESI): calcd for $C_{10}H_{10}N_4O_2S$ $[M+H]^+$: 251.05972; found 251.05919.

2-(5-(Ethylthio)-2H-tetrazol-2-yl)-5-methoxybenzoic acid (30) From 2-bromo-5-methoxybenzoic acid (**20,** 200 mg, 0.87 mmol), 2-(5-(ethylthio)-2H-tetrazol-2-yl)-5-methoxybenzoic acid (66%) was obtained as yellow solid. The assay yield was 74%. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.43 (t, *J* = 7.3 Hz, 3H), 3.23 (q, *J* = 7.3 Hz, 2H), 3.93 (s, 3H), 7.22 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.54-7.57 (m, 2H), 11.40 (br s, 1H) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 14.83, 26.74, 56.05, 116.36, 118.84, 127.52, 128.03, 128.90, 160.98, 164.36, 169.25 ppm. **HRMS** (ESI): calcd for $C_{11}H_{12}N_4O_3S$ $[M+H]^+$: 281.07029; found 281.06967.

5-Bromo-2-(5-(ethylthio)-2H-tetrazol-2-yl)benzoic acid (31) From 2,5-dibromobenzoic acid (**21**, 200 mg, 0.72 mmol), 130 mg 5-bromo-2-(5-(ethylthio)-2H-tetrazol-2-yl)benzoic acid (55%) was obtained as light-yellow solid. The assay yield was 68%. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.44 (t, *J* = 7.3 Hz, 3H), 3.24 (q, *J* = 7.3 Hz, 2H), 7.61 (d, *J* = 2.1 Hz, 1H), 7.88 (d, *J* = 8.5, 2.1 Hz, 1H), 8.19 (d, *J* = 2.1 Hz, 1H), 11.22 (br s, 1H) ppm **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 14.79, 26.69, 124.81, 127.37, 127.68, 134.42, 134.44, 136.29, 165.18, 168.26 ppm. **HRMS** (ESI): calcd for $C_{10}H_9BrN_4O_2S$ $[M+H]^+$: 330.96874; found 330.96725.

2-(5-(Ethylthio)-2H-tetrazol-2-yl)-4,5-difluorobenzoic acid (32) From 2-bromo-4,5-difluorobenzoic acid (**22**, 200 mg, 0.84 mmol), 130 mg 2-(5-(ethylthio)-2H-tetrazol-2-yl)-4,5-difluorobenzoic acid (54%) was obtained as yellow solid. The assay yield was 66%. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.44 (t, J = 7.3 Hz, 3H), 3.25 (q, J = 7.3 Hz, 2H), 7.59 (dd, J = 9.3, 6.5 Hz, 1H), 7.96 (t, J = 8.7 Hz, 1H), 11.34 (br s, 1H) ppm. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ -130.74 (d, J = 21.3 Hz), -125.87 (d, J = 21.3 Hz) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 14.75, 26.63, 116.63 (d, J = 21.2 Hz), 120.99 (d, J = 20.3 Hz), 123.43, 132.46 (dd, J = 8.2, 3.7 Hz), 150.42 (dd, J = 148.3, 13.0 Hz), 152.99 (dd, J = 152.2, 13.0 Hz), 165.36, 167.39 ppm. **HRMS** (ESI): calcd for $C_{10}H_8F_2N_4O_2S$ $[M+H]^+$: 287.04088; found 287.04013.

2-(5-(Ethylthio)-2H-tetrazol-2-yl)-5-nitrobenzoic acid (33) From 2-bromo-5-nitrobenzoic acid (**23,** 500 mg, 2.03 mmol), 120 mg 2-(5-(ethylthio)-2H-tetrazol-2-yl)-5-nitrobenzoic acid (20%) was obtained as light brown solid. The assay yield was 20%. Conversion was about 48% based on HPLC with UV detector set at 210 nm. The reaction of 2-iodo-5-nitrobenzoic acid (**29**, 500 mg, 1.7 mmol) gave 110 mg **33** (22%) as yellow solid. The assay yield was 26%, LCMS indicated about 55% conversion. **^{1}H-NMR** (400 MHz,

$CDCl_3$): δ 1.47 (t, *J* = 7.3 Hz, 3H), 3.29 (q, *J* = 7.3 Hz, 2H), 8.06 (d, *J* = 8.8 Hz, 1H), 8.60 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.85 (d, *J* = 2.3 Hz, 1H), 9.82 (br s, 1H) ppm. **^{13}C-NMR** (101 MHz, DMSO-d_6): δ 15.30, 26.62, 125.96, 127.97, 128.03, 130.09, 138.43, 148.79, 164.91, 164.99 ppm. **HRMS** (ESI): calcd for $C_{10}H_9N_5O_4S$ $[M+H]^+$: 296.04480; found 296.04410.

2-(5-(Ethylthio)-2H-tetrazol-2-yl)-6-iodobenzoic acid (34) From 2-bromo-6-iodobenzoic acid (**24**, 200 mg, 0.6 mmol), 60 mg 2-(5-(ethylthio)-2H-tetrazol-2-yl)-6-iodobenzoic acid (26%) was obtained as yellow solid. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.47 (t, *J* = 7.3 Hz, 3H), 3.27 (q, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 1H), 8.02–8.06 (m, 2H), 8.60 (s, 1H) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 14.83, 26.66, 93.83, 122.12, 131.59, 132.54, 133.44, 140.92, 165.54, 170.32 ppm. **HRMS** (ESI): calcd for $C_{10}H_9IN_4O_2S$ $[M+H]^+$: 376.95637; found 376.95538.

4-Bromo-2-(5-(Ethylthio)-2H-tetrazol-2-yl) benzoic acid (35) From 4-bromo-2-iodobenzoic acid **25** (200 mg, 0.6 mmol), 88 mg 4-bromo-2-(5-(ethylthio)-2H-tetrazol-2-yl) benzoic acid (44%) was obtained as yellow solid. The assay yield was 52%. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.44 (t, *J* = 7.3 Hz, 3H), 3.25 (q, *J* = 7.3 Hz, 2H), 7.81 (dd, *J* =

8.4, 1.6 Hz, 1H), 7.89 (d, J = 1.6 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 11.19 (s, 1H) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 14.80, 26.67, 124.94, 127.61, 129.31, 132.79, 133.95, 136.35, 165.25, 169.25 ppm. **HRMS** (ESI): calcd for $C_{10}H_9BrN_4O_2S$ $[M+H]^+$: 330.96874; found 330.96719.

5-Chloro-2-(5-(ethylthio)-2H-tetrazol-2-yl)benzoic acid (36)[18] From 5-chloro-2-iodobenzoic acid (**26**, 1 g, 3.54mmol), 0.54 g 5-chloro-2-(5-(ethylthio)-2H-tetrazol-2-yl)benzoic acid (54%) was obtained as off-white solid. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.44 (t, J = 7.3 Hz, 3H), 3.25 (q, J = 7.3 Hz, 2H), 7.68 (d, J = 8.5 Hz, 1H), 7.73 (dd, J = 8.5, 2.3 Hz, 1H), 8.05 (d, J = 2.2 Hz, 1H), 10.13 (s, 1H) ppm. **^{13}C-NMR** (101 MHz, DMSO-d_6): δ 15.38, 26.58, 127.90, 128.87, 129.75, 130.03, 133.41, 135.45, 162.93, 166.29 ppm. **HRMS** (ESI): calcd for $C_{10}H_9ClN_4O_2S$ $[M+H]^+$: 285.02075; found 285.02014.

2-(5-(Ethylthio)-2H-tetrazol-2-yl)-5-fluorobenzoic acid (37)[18] From 5-fluoro-2-iodobenzoic acid (**27**, 1 g, 3.76 mmol), 0.63 g 2-(5-(ethylthio)-2H-tetrazol-2-yl)-5-fluorobenzoic acid (62%) was obtained as light-yellow solid. The assay yield was 71%. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.43 (t, J = 7.3 Hz, 3H), 3.24 (q, J = 7.3 Hz, 2H), 7.50-

7.42 (m, 1H), 7.70 (dd, J = 8.8, 4.6 Hz, 1H), 7.79 (dd, J = 8.1, 2.6 Hz, 1H), 11.53 (s, 1H) ppm. **^{19}F-NMR** (376 MHz, $CDCl_3$): δ -106.7 ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 14.78, 26.68, 118.85 (d, J = 25.3 Hz), 120.41 (d, J = 23.0 Hz), 128.60 (d, J = 8.7 Hz, 2C), 131.96 (d, J = 3.5 Hz), 162.99 (d, J = 254.5 Hz), 164.94, 168.04 ppm. **HRMS** (ESI): calcd for $C_{10}H_9FN_4O_2S$ $[M+H]^+$: 269.05030; found 269.04971.

2-(5-(Ethylthio)-2H-tetrazol-2-yl)-5-methylbenzoic acid (38) From 2-iodo-5-methylbenzoic acid (**28**, 1 g, 3.82 mmol), 0.76 g 2-(5-(ethylthio)-2H-tetrazol-2-yl)-5-methylbenzoic acid (73%) was obtained as white solid. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.44 (t, J = 7.3 Hz, 3H), 2.51 (s, 3H), 3.24 (q, J = 7.3 Hz, 2H), 7.51-7.59 (m, 2H), 7.89 (s, 1H), 9.71 (s, 1H) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 14.68, 21.21, 26.82, 125.59, 126.41, 132.32, 133.45, 134.32, 142.01, 164.61, 170.08 ppm. **HRMS** (ESI): calcd for $C_{11}H_{12}N_4O_2S$ $[M+H]^+$: 265.07537; found 265.07483.

5-Chloro-2-(2H-tetrazol-2-yl)benzoic acid (50)

Method A To a 10 mL flask were charged with 10% Pd/C (20 mg), 5-chloro-2-(5-(ethylthio)-2H-tetrazol-2-yl)benzoic acid (**36,** 200 mg, 0.70 mmol), and THF (1.0 mL) under nitrogen. The mixture was placed in a 0 ºC bath, treated with triethylsilane (490

mg, 4.22 mmol) and warmed to room temperature slowly. After stirred for overnight the mixture was filtered and the filtrate was purified by Combi-flash (ACN:H_2O with 0.05% TFA 30%-60%, 30 min). Compound **50** (120 mg, 76%) was obtained as white solid.

Method B To a 10 mL 2-neck RB flask was charged with 10% Pd/C (100 mg) and **36** (100 mg, 0.35 mmol) in THF (1.0 mL). The mixture was placed in a 0 ºC bath, treated with triethylsilane (245 mg, 2.11 mmol) and warmed to room temperature slowly. After agitation overnight, the mixture was filtered. The assay yield of **50** was 91% by HPLC.

Method C A solution of 5-chloro-2-(5-(ethylthio)-2H-tetrazol-2-yl)benzoic acid (**36**, 100 mg, 0.35 mmol) was dissolved in 1 mL water with 2 eq iPr_2NH. The solution was added dropwise to 350 mg Raney Ni in 1 mL water. The mixture was warmed to 50 °C slowly and agitated for 4 h. LCMS showed complete reaction. The mixture was filtered and the assay yield for **50** was 42%.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.5 Hz, 1H), 7.75 (dd, J = 8.5, 2.3 Hz, 1H), 8.08 (d, J = 2.3 Hz, 1H), 8.72 (s, 1H), 9.81 (s, 1H) ppm. **^{13}C-NMR** (101 MHz, DMSO-d_6): δ 128.65, 130.66, 130.91, 132.98, 133.82, 136.30, 154.05, 165.23 ppm. **HRMS** (ESI): calcd for $C_8H_5ClN_4O_2$ $[M+H]^+$: 225.01738; found 225.01685

5-Fluoro-2-(2H-tetrazol-2-yl)benzoic acid (51)

White solid (method A, 39%; method B, 88%; method C, 75%) ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.48 (ddd, *J* = 8.8, 7.2, 2.9 Hz, 1H), 7.70 (dd, *J* = 8.8, 4.7 Hz, 1H), 7.82 (dd, *J* = 8.2, 2.9 Hz, 1H), 8.72 (s, 1H), 9.12 (s, 1H) ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ -106.55 ppm. ^{13}C-NMR (101 MHz, DMSO-d_6): δ 118.02 (d, *J* = 25.0 Hz), 120.02 (d, *J* = 23.2 Hz), 129.61 (d, *J* = 9.2 Hz), 131.65 (d, *J* = 3.0 Hz), 131.94 (d, *J* = 8.0 Hz), 153.90, 163.03 (d, *J* = 250.8 Hz), 165.21 ppm. HRMS (ESI): calcd for $C_8H_5FN_4O_2$ $[M+H]^+$: 209.04693; found 209.04652.

5-Methyl-2-(2H-tetrazol-2-yl)benzoic acid (52)

White solid (method A, 49%; method B, 87%; method C, 53%) ^{1}H-NMR (400 MHz, $CDCl_3$) : δ 2.53 (s, 3H), 7.56 (s, 2H), 7.92 (s, 1H), 8.69 (s, 1H) ppm. ^{13}C-NMR (101 MHz, DMSO-d_6): δ 21.08, 126.80, 128.85, 131.44, 133.04, 133.47, 141.99, 153.77, 166.43 ppm. HRMS (ESI): calcd for $C_9H_8N_4O_2$ $[M+H]^+$: 205.07200; found 205.07161.

ACKNOWLEDGMENT. We thank Robert Reamer and Lisa DiMichele for NMR analysis, Andrew Brunskill for X-ray analysis, Khateeta Emerson for calorimetry, Dave Tschean and Jaume Balsells, Steven Oliver, and Jing Li for helpful discussions.

Supporting Information Available. HPLC conditions for the preparation of compound **1**, crystallographic information, copies of ^{1}H and ^{13}C NMR, ^{19}F NMR when applicable, 2D NMR, HMBC, HSQC when applicable, LCMS of the purified samples for compounds **1, 16, 30-38, 50, 51, 52,** DSC data for compounds **1**, **15**, **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: zhiguo_song@merck.com * E-mail: peter_maligres@merck.com

REFERENCES

1. (a) Butler, R. N. Tetrazoles "Comprehensive Heterocyclic Chemistry" Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, UK, **1996**; Vol. 4. 621-678. (b) Ostrovskii, V. A.; Koldobskii, G. I.; Trifonov, R. E. Tetrazoles

"Comprehensive Heterocyclic Chemistry III" Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K. Eds.; Elsevier: Oxford. **2008**, Vol. 6, 257-423.

2. (a) Herr, R. J. 5-Substituted-1H-tetrazoles as Carboxylic Acid Isosteres: Medicinal Chemistry and Synthetic Methods *Bioorg. Med. Chem.* **2002,** *10*, 3379-3393. (b) Myznikov, L. V.; Hrabalek, A.; Koldobskii, G. I. Drugs in the Tetrazole Series *Chem. Heterocycl. Compd.*, **2007**, *43*, 1-9. (c) Ostrovskii, V. A., Trifonov, R. E., Popova, E. A. Medicinal Chemistry of Tetrazoles *Russ. Chem. Bull. Int. Ed.*, **2012**, *61*, 768-780.

3. Synthesis of different substitution patterns (a) Koldoboskii, G. I.; Kharbash, R. B. 2-Substituted and 2,5-Disubstituted Tetrazoles *Russ. J. Org. Chem.* **2003**, *39*, 489-505. (b) Koldoboskii, G. I. Strategies and Prospects of Functionalizing Tetrazoles *Russ. J. Org. Chem.* **2006**, *42*, 469-486. (c) 5-Substituted: Demko, Z. P.; Sharpless, K. B. Preparation of 5-Substituted 1H-Tetrazoles from Nitriles in Water *J. Org. Chem.* **2001**, *66,* 7945-7950.

4. For examples of Ullman-type couplings, see: (a) Ley, S. V.; Thomas, A. W. Modern Synthetic Methods for Copper-Mediated C(aryl)-O, C(aryl)-N, and C(aryl)-S Bond Formation *Angew. Chem., Int. Ed.* **2003**, *42*, 5400-5449. (b) Shafir, A.; Buchwald, S. L. Highly Selective Room-Temperature Copper-Catalyzed C−N Coupling Reactions *J. Am. Chem. Soc*. **2006**, *128*, 8742-8743. (c) Benson, F. R. The Chemistry of the Tetrazoles *Chem. Rev.* **1947**, *41,* 1-61.

5. Kuduk, S. D.; Skudlarek, J. W. 2-Pyridyloxy-4-ether Orexin Receptor Antagonists WO2014137883, **2014.**

6. (a) Ito, S.; Tanaka, Y.; Kakehi, A.; Kondo, K.-I. New Synthesis of 2,5-Disubstituted Tetrazoles via 1,5-Dipolar Cyclization *Chem. Lett.* **1973**, 1071-1072. (b) Ito, S.; Tanaka, Y.; Kakehi, A.; Kondo, K.-I. Facile Synthesis of 2,5-Disubstituted Tetrazoles by Reaction of Phenylsulfonylhydrazones with Arenediazonium Salts. *Bull. Chem. Soc. Jpn*. **1976**, 49, 1920-1923. (c) Ito, S.; Tanaka, Y.; Kakehi, A.; Kawahata, M. Formation of 5-Phenyltetrazole from N2-Benzoyl-N4-(phenylsulfonyl)benzohydrazide Hydrazone *Bull Chem. Soc. Jpn*.

1978, *51*, 953-954. (d) Ito, S.; Tanaka, Y.; Kakehi, A. Characteristic Behavior of N-(Phenylsulfonyl)benzohydrazonoayl Azide: Base-Induced Decomposition to Benzonitrile and Cyclization to a Tetrazole *Chem. Lett.* **1982**, *1*, 59-60. (e) Doyle, M. P.; Bryker, W. J. Alkyl Nitrite-Metal Halide Deamination Reactions. 6. Direct Synthesis of Arenediazonium Tetrafluoroborate Salts from Aromatic Amines, tert-Butyl Nitrite, and Boron Trifluoride Etherate in Anhydrous Media *J. Org. Chem.* **1979**, *44*, 1572-1574. (f) Blankley, C. J.; Sauter, F. J.; House, H. O. Crotyl Diazoacetate *Org. Synth*. **1969**, *49*, 22-26. (g) Huisgen, R.; Fliege, W.; Kolbeck, W. 1,3-Dipolare Cycloadditionen, 87. Zur Kenntnis des N-Phenylnitrilimins *Chem. Ber.* **1983**, *116*, 3027-3038.

7. (a) Patouret, R.; Kamenecka, T. M. Synthesis of 2-Aryl-2H-Tetrazoles via a Regioselective [3+2] Cycloaddition Reaction *Tetrohedron Lett*. **2016**, *57*, 1597-1599. (b) Li, Z.; Qian, L.; Li, L.; Bernhammer, J. C.; Huynh, H. V.; Lee, J.-S.; Yao, S. Q. Tetrazole Photoclick Chemistry: Reinvestigating Its Suitability as a Bioorthogonal Reaction and Potential Applications *Angew. Chem. Int. Ed.* **2016**,

55, 2002-2006. (c) Slow addition minimizes side reactions and gives cleaner reaction profile.

8. (a) Beletskaya, I. P.; Davydov, D. V.; Gorovoy, M. S. Palladium- and Copper-catalyzed Selective Arylation of 5-Aryltetrazoles by Diaryliodonium Salts *Tetrahedron Lett.* **2002**, *43*, 6221-6223. (b) Davydov, D. V.; Beletskaya, I. P.; Semenovb, B. B.; Smushkevich, Y. I. Regioselective Arylation of N-Tributylstannylated 5-Substituted Tetrazoles by Diaryliodonium Salts in the Presence of $Cu(OAc)_2$ *Tetrahedron Lett*. **2002**, *43*, 6217-6219. (c) Onaka, T.; Umemoto, H.; Miki, Y.; Nakamura, A.; Maegawa, T. $[Cu(OH)(TMEDA)]_2Cl_2$-Catalyzed Regioselective 2-Arylation of 5-Substituted Tetrazoles with Boronic Acids under Mild Conditions *J. Org. Chem.* **2014**, *79*, 6703−6707.

9. S_NAr type displacement of activated aryl fluorides by 5-substituted tetrazole heated by microwave irradiation were reported with modest selectivity toward N2 position: Efimova,Y. A.; Artamonova, T. V.; Koldobskii, G. I. Microwave-assisted Arylation of 5-Substituted Tetrazoles *Russ. J. Org. Chem.* **2010**, *46*, 612-614.

10. (a) Mozingo, R.; Wolf, D. E.; Harris, S. A.; Folkers, K. Hydrogenolysis of Sulfur Compounds by Raney Nickel Catalyst *J. Am. Chem. Soc*. **1943**, *65*, 1013-1016. (b) Howard, G. A.; Lythgoe, B.; Todd, A. R. Experiments on the Synthesis of Purine Nucleosides. Part XI. The Synthesis of 9-d-Xylopyranosido-2-methylthioadenine and Its Conversion into 9-d-Xylopyranosidoadenine *J. Chem. Soc.* **1945**, 556-561. (c) Shafer, C. M.; Molinski, T. F. Monosubstituted Oxazoles. 1. Synthesis of 5-Substituted Oxazoles by Directed Alkylation *J. Org. Chem.* **1998**, *63*, 551-555. (d) Graham T. H.; Liu, W.; Shen, D.-M. A Method for the Reductive Scission of Heterocyclic Thioethers *Org. Lett.* **2011**, *13*, 6232-6235. (e) Matsumura, T.; Niwa, T.; Nakada, M. Pd-Catalyzed Reductive Cleavage of Alkyl Aryl Sulfides with Triethylsilane that is Accelerated by Trialkylsilyl Chloride *Tetrahedron Lett.* **2012**, *53*, 4313-4316 and references cited there in.

11. The ligands screened include: TMEDA, diaminocyclohexane, 2,2'-bipyridyl, 4,4'-di-*t*-butyl-2,2'-bipyridyl, 1,10-phenanthroline, 2,9-dimethyl-1,10-phenanthroline, 3,4,7,8-tetramethyl-1,10-phenanthroline, terpyridine, tris-t-butyl terpyridne, 8-

hydroxyquinoline, N,N-dimethylglycine, L-proline, picolinic acid, thiophene-2-carboxylic acid, *N,N*-diethylsalicylamide, salicylaldoxime, Chxn-Py-Al, 1,3-di(2'-pyridyl)-1,3-dione, $Cu(TMHD)_2$, Cu(2-acetylcyclohexanonate)$_2$, Cu(2-isobutyrylcyclohexanonate)$_2$.

12. Methyl esters of 2-fluorobenzoic acid and 2-fluoro-5-bromobenzoic acid were screened for S_NAr reaction with 5-ethylthio tetrazole and found to be unreactive.

13. 2-Bromobenzoic acid gave a slower rate and 2-chlorobenzoic acid was even less reactive.

14. Base screen included the following bases: Li_2CO_3, Na_2CO_3, K_2CO_3, Cs_2CO_3, K_3PO_4, LiOH, $NaHCO_3$, KF, KOAc, TMEDA, DIPEA, N-ethylmorpholine, N-ethylpiperidine, DBU, tetramethylguanidine, 2,6-lutidine.

15. A group of 42 solvents were screened : toluene, *o*-xylene, *p*-xylene, fluorobenzene, trifluoromethylbenzene, cyclopentyl methyl ether, cineol, anisole, DEM (diethoxymethane), DMP (2,2-dimethoxypropane), THF, 2-MeTHF, THP,

DHP, DME, diglyme, triglyme, DEE (1,2-diethoxyethane), dioxane, dioxalane, *N*-methyl morpholine, triethylamine, *N,N*-diisopropylethylamine, $PhNMe_2$, pyridine, 2-picoline, 4-picoline, *N, N, N', N'*-tetramethylethylenediamine, *N*-methylimidazolinone, MeCN, PhCN, DMF, DMAc, NMP, Tetramethylurea, DMI, DMPU, $(EtO)_3CH$, *t*-AmylOH, DMSO, sulfolane, PhSMe. The reactions were run at 85 °C for 18 h with 0.1 eq $Cu(MeCN)_4PF_6$, 0.15 eq 2,2'-bipyridine, 3 eq K_3PO_4.

16. Crystallographic information has been deposited with the Cambridge Crystallographic Database and is available online at http://www.ccdc.cam.ac.uk/Community/Requestastructure/Pages/DataRequest.aspx. See CCDC deposition 1876146.

17. The gas evolved was believed to be ethane since it has a density similar to air (excludes butane) and did not react with bromine or aqueous permanganate (excludes olefins such as ethylene). Absorption of this gas into $CDCl_3$ followed by NMR analysis showed only a singlet at 0.87 ppm for ethane. A sample of the nickel residue after filtration from the reaction mixture was acidified with aq HCl

resulting in the evolution of a gas with the typical odor of H_2S. Further proof verifying the gas to contain H_2S was obtained by exposing filter paper strips moistened with aqueous $Pb(OAc)_2$ and with aqueous $Cd(OAc)_2$ resulting in black (PbS) and yellow (CdS) colors respectively. Therefore, the sulfur is bound to the nickel as sulfide.

18. Kamenecka, T. M.; Holenz, J.; Wesolowski, S.; He, Y.; Buerli, R. "Halo-substituted Piperidines as Orexin Receptor Modulators and Their Preparation" WO 2017139603, 2017