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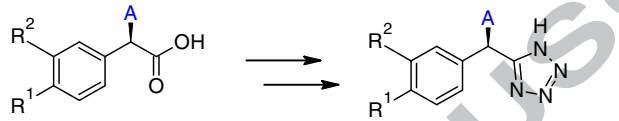

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Retention of stereochemistry in the microwave assisted synthesis of 1*H*-tetrazole bioisosteric moiety from chiral phenyl-acetic acid derivatives

Mara Tomassetti[a], Michela Fanì[b], Gianluca Bianchini[a], Sandra Giuli[a], Andrea Aramini[a,b], Sandro Colagioia[a], Giuseppe Nano[a] and Samuele Lillini[b,*]

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ABSTRACT

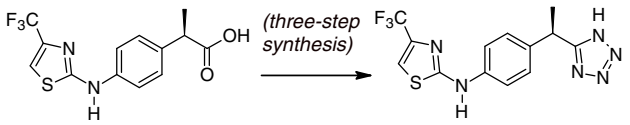
Chiral substituted phenylethyl-1*H*-tetrazoles were build-up from the corresponding carboxylic acid derivatives by a useful three-step synthesis. The procedure, that preserves the chiral center from racemization, was successfully applied to a selection of several hit compounds by conversion of the carboxylic acid moiety to the nitrile derivatives and subsequent reaction with trimethylstannyl azide, under microwave conditions. A useful application to the corresponding tetrazole analogue has been found also in the conversion of the aminoacidic moiety like (*R*)-N-Cbz-phenylglycine showing a wide potential synthetic application.

Inflammatory and neuropathic pain are the most prevalent types of pathological pain and represent important health problems. Whereas inflammatory pain is one of the classical symptoms of the inflammatory process, neuropathic pain arises from any of multiple nerve lesions or diseases with symptoms including hyperalgesia or allodynia.[1] Some of the most powerful painkillers, including opioids and non-steroidal anti-inflammatory drugs, are generally not selective, only partially effective and prolonged exposure can cause side effects.[2] As a result, there is a continuous effort to identify novel therapeutics for pain control with alternative mechanism of action and that elicit fewer side effects.

Inflammatory mediators, including cytokines/chemokines, play a critical role in the pathogenesis of inflammatory and neuropathic pain.[3] Emerging evidences suggest that C5a, the anaphylatoxin produced by the complement activation, has potent nociceptive activity in several models of inflammatory and neuropathic pain by interacting with its selective receptor C5aR.[4] C5aR belongs to the class A subfamily of the G protein-coupled receptors (GPCR)[5] and is widely expressed in immune cells, including neutrophils (PMN), monocytes, microglia, and in non-immune cells, including neurons in the central nervous system (CNS) and dorsal root ganglia (DRG).[6]

As for other peptidergic GPCRs, the efforts to identify small molecular weight C5aR antagonists have led to a limited number of molecules, mostly lacking adequate potency and selectivity.[7]

During our discovery programs, we selected a novel class of (*R*)-4-(heteroaryl)phenylpropionic derivatives, typified by compound DF2703Y (**1a**, Figure 1), which shows strong selectivity and potency in inhibiting C5a-induced neutrophils chemotaxis. Lead optimization program has permitted the investigation of large series of carboxylic acid bioisosteres[8] identifying the tetrazole group as the best moiety and DF3966Y (**4a**, IC_{50} = 50nM, Figure 1) as the Lead Compound in terms of pharmacological profile (ADME and PK), maintaining potency and selectivity properties.



DF2703Y (**1a**) DF3966Y (**4a**)

Figure 1. Conversion of the carboxylic acid moiety to the tetrazole, the corresponding bioisostere.

The addition of azide ion to nitriles is the most convenient route to obtain 5-substituted 1*H*-tetrazoles. Cyano derivatives are easily available by conversion of the carboxylic acid moieties to the corresponding amides and subsequent dehydration (Scheme 1). The extreme toxicity, the low boiling point (37°C) and the explosive nature of the hydrazoic acid (HN_3) prevent its use as free acid.[9] Comparatively safe azide's sources have been introduced in the last few decades, the most common are, besides of the sodium azide (NaN_3), tin, aluminum and silicon azides[10] which are employed in a wide range of reaction conditions.

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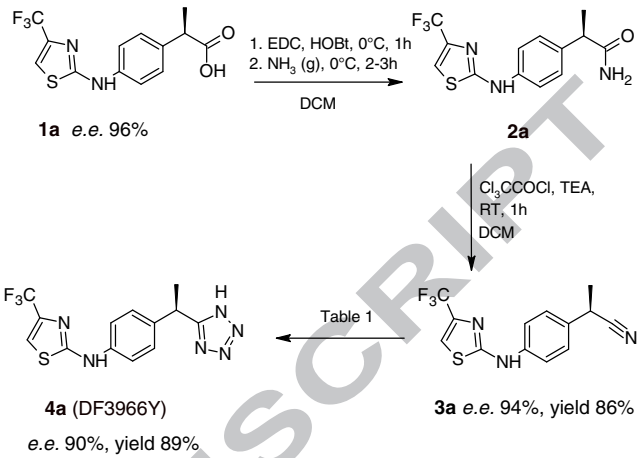
It is well-known that azide salts can engage nitriles[11] at elevated temperatures to yield tetrazoles, however, there is continuous debate on the mechanism of the reaction. Despite of numerous examples reported in the literature, there are no papers describing the synthesis of phenylethyl-1*H*-tetrazole derivatives from *chiral* phenylethyl-nitriles with retention of stereochemical configuration.

Herein, we present a novel method for the synthesis of chiral phenylethyl 1*H*-tetrazoles using trialkylstannyl-azides as the source of azide under microwave conditions.

The synthesis of our target compound **4a** is shown in Scheme 1. Starting from carboxylic acid **1a,** amide **2a** was obtained via activation with EDC, HOBt in DCM and subsequent bubbling with gaseous NH_3 at low temperature (0°C).[12] Extremely convenient reaction conditions were found in the use of trichloroacetyl chloride and TEA in DCM for the conversion of amide **2a** to the corresponding nitrile **3a**. Compound **3a** was obtained with 94% of enantiomeric excess in 86% yield (Scheme 1).[13] Some other dehydrating reagents such as thionyl chloride, phosgene and phosphorus oxychloride, used under classical reaction conditions provided comparable yields but lower optical purity.

The enantiomeric excess values were evaluated comparing the chiral compound with its corresponding racemate by chiral HPLC assays. An extensive study of reaction conditions has been performed in the synthesis of our lead compound **4a** (DF3966Y, Scheme 1) starting from the easily racemizable **3a** (Table 1).



Scheme 1. Synthesis of the target compound **4a** (DF 3966Y)

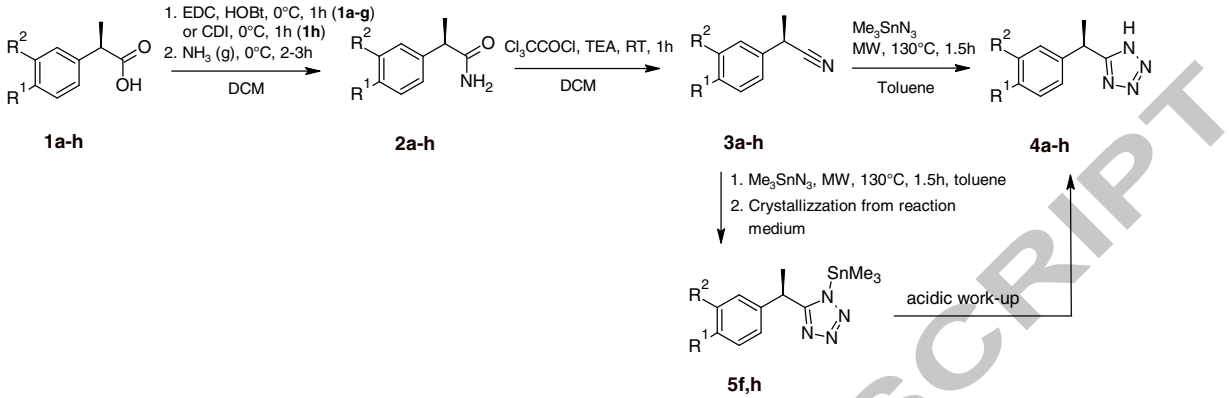
Table 1. Study of reaction conditions in the tetrazole synthesis

Entry	Azide source	Solvent	Conditions	Conversion (%)	Yield (%)	% *e.e.*
1	$TMSN_3$(9eq), TBAF(9eq)	THF	18h, 85°C	80	60	0
2	$TMSN_3$(1eq), TBAF(1eq)	THF	MW 1h, 130°C	100	76	0
3	NaN_3(1eq)	NMP/AcOH/H_2O; 7:2:1 (Vol)	MW 1h, 150°C	100	92	0
4	NaN_3(4eq)	NMP/AcOH; 7:3 (Vol)	MW 1h, 150°C	82	73	0
5	NaN_3(1.05eq) , NH_4Cl(1.05eq)	DMF	MW 1h, 150°C	44	18	0
6	NaN_3(1.1eq), $ZnBr_2$(1eq)	IPA/ H_2O/NMP; 9:0.5:0.5 (Vol)	MW 1h, 120°C	45	35	0
7	Me_3SnN_3(1.5eq)	toluene	MW 1.5h, 130°C	100	89	90
8	Me_3SnN_3(1.5eq)	toluene	24 h, reflux	50	45	80

It was clearly evident from the literature that a high yielding and fast tetrazole formation would have to involve a high temperature regime and pressure control, in an environmentally safe reactor. In order to improve these preparation protocols, we performed our study under microwave irradiation, using this powerful technique to accelerate the thermally-driven chemical reactions. We began our investigations by evaluating several reported methods of tetrazole synthesis, with the aim of finding the one that would be appropriate to obtain the target compound in good yield and most of all, with high enantiomeric excess (Table 1). Under our reaction conditions screening, three different azide's sources were used, moving from $TMSN_3$/TBAF in THF (Entries 1 and 2), in which complete conversion and good yield were obtained (Entry 2) to NaN_3 in a mixture of polar solvents (Entries 3-6). It is noteworthy that the reaction carried out in a conventional heating required longer times and an excess of reactants to obtain a good conversion (Entry 1).

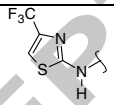
The complete conversion and excellent yield were performed using NaN_3 in NMP/AcOH/H_2O heated at 150°C under microwave irradiation (Entry 3). All reaction conditions in Table 1 (Entries 1-6) lead to complete racemization. As an alternative to inorganic azide salts, the trimethylstannyl azide (Me_3SnN_3) was adopted (Entry 7). This reagent offers several advantages over the other reagents including better solubility in organic solvents and it is comparatively safer to use. The reaction was carried out in toluene using 1.5 equivalents of tin reagent, heating by microwave irradiation at 130°C for 1.5h. The reaction proceeds in a high yield (89%) and with an excellent retention of configuration (90% of enantiomeric excess, see Table 1 and Table 2), proving that the reaction conditions have negligible effect on the enantiomeric purity of compound **4a**.[13] As comparison with the normal heating (Table 1, Entry 8), it should be pointed out that microwave irradiation improves yield, reaction time and markedly the optical purity.

To explore the scope and limitations of this method a significant selection of diversely substituted *chiral* phenylethyl-nitrile derivatives was synthesized starting from the corresponding carboxylic acid derivatives (Scheme 2 and Table 2). *Para* and *meta* EWGs and EDGs were chosen in order to evaluate the direct effect to the acidity of the proton at the benzylic position.



Scheme 2. Synthesis of chiral phenylethyl 1*H*-tetrazoles from *chiral* benzyl-nitriles.

Table 2. Reaction scope

Entry	Compound	R^1 (*para*)	R^2 (*meta*)	Acid (**1**)*	Amide (**2**)		Nitrile (**3**)		Tetrazole (**4**)	
				% *e.e.*	% yield	% *e.e.*	% yield	% *e.e.*	%yield	% *e.e.*
1	a		H	97	68	95	86	94	89	90
2	b		H	96	56		85		95	88
3	c	H		96	83		87		93	90
4	d		H	98	80		80		60	92
5	e	H		97	85		82		67	93
6	f	H		98	90		83	96	90	93
7	g		F	98	97		97	96	64	94
8	h	4-NO_2	H	97	86**	92**	84	70	96	0

* Optical purity of the starting materials.
** The acid **1h** was activated by CDI (1.5eq) in DCM and treated with gaseous NH_3 at low temperature (0°C).

Moderate loss of enantiomeric purity was observed for *para* and *ortho*-triflate derivatives, respectively **4b** and **4c** (Entries 2 and 3).

The method proved to be very efficient in the synthesis of a single tetrazole's enantiomer structurally related to some active pharmaceutical ingredients, such as: Ibuprofen **4d** (Table 2, entry 4), Ketoprofen **4f** (Entry 6) and Flurbiprofen **4g** (Entry 7). A comparable result was achieved for the *meta*-alkyl compound **4e**.

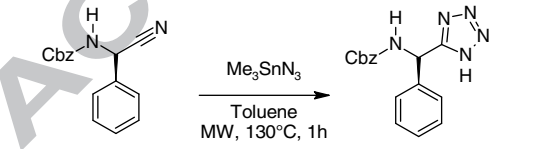
To further examine the range of applicability of this reaction, the 4-nitrophenyl derivative **4h** was synthesized. The common method used for the preparation of the amides **2a-g**, via activation by EDC/HOBt gave a complete racemization when applied to synthesis of intermediate **2h**. The mentioned amide **2h** was differently obtained with 92% e.e. by activation with CDI and subsequent bubbling with gaseous ammonia (Table 2, entry 8). A loss of optical purity occurred in the dehydration step to obtain nitrile derivatives **3h,** (70%, Table 2, Entry 8). We then applied our standard protocol with Me_3SnN_3 but tetrazole was obtained as a racemic mixture. All attempts done for the synthesis of chiral tetrazole **4h**, unfortunately failed.

In order to assess the (2*R*)-2-(4-nitrophenyl)propanenitrile (**3h**) stability without any source of azide, the compound was subjected to a set of different conditions mimicking the standard ones or testing mechanism hypotheses. Mild anhydrous acidic conditions (cat. AcOH), mild anhydrous basic (an. sodium bicarbonate), mild aqueous basic (sodium bicarbonate) and simple heating in toluene at 130°C, all led to optical purity loss. Negligible loss of enantiomeric purity was observed for the nitrile derivatives **3a**-**g** by heating at 130°C for 30 minutes.

All these tests taken together point toward tautomeric mechanisms assisting the proton abstraction that causes racemization in the 4-nitro derivative. Furthermore, the absence of a solvent capable of proton coordination indicates that intermolecular coordination between reacting nitrile molecules may play a significant role in the supposed mechanism.

Tin-tetrazole adducts **5f,h** were isolated directly from the reaction medium: after 1.5 hours of microwave heating, the mixture was cooled to room temperature and concentrated without any workup and the products crystallized.[15,16] Subsequent acidic hydrolysis of **5h,f** yielded the corresponding tetrazoles, respectively **4f** and **4h**.

Continuing the investigations in the field of the carboxylic acid replacement, the method has been successfully applied in the synthesis of the tetrazole derivative of (*R*)-*N*-Cbz-phenylglycine. Starting from chiral α-amino nitrile **6**, obtained with an e.e. of 86% (Scheme 3), tetrazole **7** was synthesized obtaining a good yield (79%) and a good enantiomeric purity (e.e. 80%). To the best of our knowledge, derivative **7** has never been obtained with an e.e. higher than 39%.[17]



6 *e.e.* 86% **7** *e.e.* 80%, yield 79%

Scheme 3. Tetrazole analogous of (*R*)-N-Cbz-phenylglycine.

As described by Sharpless and coworkers in a relevant computational study, two plausible mechanisms can be involved at the same time in the the addition of the azide ion to the nitrile leading to the tetrazole. The two considered are: a two-step mechanism, wherein the azide first nucleophilically attacks the nitrile followed by ring closure, and a concerted [2 + 3] cycloaddition.[18] In our case both mechanisms do not necessarily involve the chiral center.

Differently from the two-step mechanism, which is generally reported for azide ion in polar solvent, the concerted one is described for covalent species such as alkyl azides. In our hypothesis a greater degree of covalency in the nitrogen-metal bond of the stannylazide as compared to sodium azide,[19] presumably drives the reaction towards a 1,3-dipolar concerted cyclization, as demonstrated by the stability of the isolated intermediates **5f,h** and the use of an apolar solvent like toluene.

In summary, we have demonstrated an exceedingly simple protocol for the transformation of a wide variety of *chiral* phenylacetonitrile into the corresponding 1*H*-tetrazoles; the method has been successfully applied to an easily racemizable *alpha* amino acid. By using Me_3SnN_3 we obtained a good to high retention of configuration in high yields. The use of trimethylstannyl azide under neutral condition prevents the formation of toxic and explosive HN_3. All the reactions were carried out in a safe microwave reactor environment improving time reaction, yield and considerably the optical purity in comparison with the conventional thermal methods. Further investigation is currently in progress in order to explore the application to other *chiral* nitriles.

Acknowledgments

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12. General procedure for the synthesis of amide (**2a-g**). A solution of the (*R*)-acid **1a-g** (1.0 eq) in dry DCM (0,05 mmol/mL) was cooled to 0°C under nitrogen atmosphere. To the mixture 1.3 eq of both 1-Hydroxybenzotriazole (HOBt) and N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC) were added to the solution and the reaction was stirred for 1h and allowed to reach R.T.. The solution was cooled to 0°C again and gaseous ammonia was bubbled in the mixture until the reaction was completed. After solvent removal under reduced pressure, the residue was dissolved in ethyl acetate and the organic layer was washed with $NaHCO_3$ s.s. then with a 2M (pH = 2) sodium phosphate buffer. The organic layers were dried over anhydrous Na_2SO_4 and the solvent removed to afford amides **2a-g**. The products were directly used for the next step without further purification unless otherwise specified (see Supplementary Data). (2*R*)-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl) propanamide (**2a**). The enantiomeric excess was found by Chiral HPLC Column: Chiracel OF, elution: HEX/IPA 80:20, flow rate: 1mL/min, injected volume: 10 µL, λ: 254 nm, sample concentration 2 mg/mL (MeOH): t1= 10.31; t2= 13.86 (S/R 2.5:97.5) e.e. 95%. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm) 1.30 (d, J=7.03 Hz, 3 H), 3.53 (q, J=7.03 Hz, 1 H), 6.80 (br. s., NH), 7.22 - 7.32 (m, 2 H), 7.34 (br. s., NH), 7.42 - 7.56 (m, 2 H), 7.63 (br s, 1 H), 10.52 (s, NH). LC-MS(ESI): $[M+H]^+$ *m/z* 316.01. $[\alpha]_D^{20}$ (c = 1.0 in MeOH) = -17.9°.

13. General procedure for the synthesis of nitriles (**3a-h**). To a solution of 2 in dry DCM (0.05 mmol/mL) TEA (2.0 eq) was added and the mixture was cooled to 0°C and stirred for 15 min under nitrogen atmosphere. A solution of trichloroacetyl chloride (2.0 eq) in dry DCM (1.0 mmol/0.6 mL) was added dropwise and the reaction was allowed to reach room temperature and stirred for 1h. The reaction was quenched with water and the organic layer was separated. The aqueous layer was extracted again with ethyl acetate (2×10 mL) and the organic layers were collected, washed with brine (1×10 mL) and dried over anhydrous Na_2SO_4. After solvent removal, nitrile 3 was isolated by purification on silica gel.
(2R)-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl) propanenitrile (**3a**). The enantiomeric excess was determined by Chiral HPLC Coloumn: PHENOMENEX LUX AMYLOSE-2, gradient: n-hexane/isopropyl alcohol 80:20, flow rate: 0.5 mL/min, Volume of injection: 2 µL, λ: 300 nm, sample concentration 1.7 mg/mL: t1= 8.62 min; t2= 9.15 min (S/R 3:97) e.e. 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.66 (d, J=7.28 Hz, 3 H) 3.91 (q, J=7.28 Hz, 1 H) 7.09 (q, J=1.00 Hz, 1 H) 7.34 - 7.43 (m, 4 H) 7.51 - 7.67 (br s, 1 H); LC-MS(ESI): $[M+H]^+$ m/z 297.97, $[M-H]^-$ *m/z* 295.94. $[\alpha]_D^{20}$ (c = 2.0, CH_3OH) = +7.5°.

14. General procedure for the synthesis of 1H-tetrazol-derivatives (**4a-h** and **7**). In a MW vial, the nitrile 3 was dissolved in toluene (0.20 mmol/ mL) and the trimethylstannyl azide (1.5 eq.) was added to the solution. The mixture was irradiated in a microwave apparatus at 130°C for 1.5h. The solvent was removed under vacuum and an aqueous solution of 1N HCl (1mL/ 0.10 mmol of substrate) was added to the crude. The suspension was stirred for 1h at r.t. and the product extracted with ethyl acetate (2 x 25 mL). The collected organic layers were washed with water (2 x 10 mL) and brine (1 x 10 mL), dried over anhydrous Na_2SO_4, and the solvent removed under reduced pressure. Tetrazoles **4** were purified on silica gel as specified in each of the following examples.
N-{4-[(1R)-1-(1H-tetrazol-5-yl)ethyl]phenyl}-4-(trifluoromethyl)-1,3-thiazol-2-amine **4a**. The enantiomeric excess was determined by Chiral HPLC Coloumn: CHIRACEL OJ, gradient: n-hexane/isopropyl alcohol 90:10 + 0.5% AcOH, flow rate: 1 mL/min, injection volum: 2 µL, λ: 300 nm, sample concentration 2 mg/1mL: t1= 65.5 min; t2= 85.3 min (R/S 92:8) e.e. 84%. ^{1}H-NMR (DMSO-d6) δ (ppm): 1.65 (d, J = 7.2 Hz, 3H), 4.51 (q, J = 7.3 Hz, 1H), 7.24 (d, J = 8.6 Hz, 2H), 7.53 (d, J = 8.6 Hz, 2H), 7.64 (s, 1H), 10.6 (s, 1H). LC-MS(ESI): $[M+H]^+$ *m/z* 340.93, $[M-H]^-$ m/z 338.99. HRMS (ESI) calc'd for $C_{13}H_{12}F_3N_6S$ $[M+H]^+$ *m/z* 341.0791, found 341.0793. $[\alpha]_D^{20}$ (c = 2.0, MeOH) = -12.9°.

15. Synthesis of **5f** (1R)-phenyl(3-(1-(2-trimethylstannyl)-2H-tetrazol-5-yl)ethyl)phenyl)phenyl) methanone.
The nitrile **3f** (0.150 g, 0.64 mmol, 1.0 eq) was dissolved in toluene (3.2 mL, 0.20 mmol/ mL) in a MW vial. Trimethylstannyl azide (0.197 g, 0.957 mmol, 1.5 eq) was added to the solution and the reaction was irradiated in a microwave apparatus at 130°C for 1.5h. The solvent was evaporated and the white precipitate was triturated in n-hexane stirring 1h. This solid was characterized by NMR. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.56 (br. s., 9 H) 1.62 (d, J=7.2 Hz, 2 H) 4.49 (q, J=7.2 Hz, 1 H) 7.34 - 7.85 (m, 8 H).

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