

# Highly regioselective Synthesis of 1-(5-Trichloromethyl-5-hydroxy-4,5-dihydroisoxazole-3-methylene)-5-phenyl-1*H*-1,2,3-triazoles

Marcos A. P. Martins,<sup>\*a</sup> Daniel J. Emmerich,<sup>b</sup> Adilson P. Sinhorin,<sup>c</sup> Marcelo Rossatto,<sup>a</sup>  
Clarissa P. Frizzo,<sup>a</sup> Helio G. Bonacorso,<sup>a</sup> and Nilo Zanata<sup>a</sup>

<sup>a</sup> Núcleo de Química de Heterociclos (NUQUIMHE), Departamento de Química, Universidade Federal de Santa Maria, 97105-900, Santa Maria, RS, Brasil

<sup>b</sup> Departamento de Química, Universidade Regional Integrada do Alto Uruguai e das Missões, Erechim, RS, Brasil; Departamento de Química, <sup>c</sup>Universidade Federal do Mato Grosso, Sinope, MT, Brasil

E-mail: [mmartins@base.ufsm.br](mailto:mmartins@base.ufsm.br)

Dedicated to Prof. Oleg Kulinkovich on the occasion of his 60<sup>th</sup> birthday

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## Abstract

A convenient method to obtain a series of 1-(5-hydroxy-5-trichloromethyl-4,5-dihydroisoxazole-3-methylene)-5-phenyl-1*H*-1,2,3-triazoles by a regioselective cycloaddition reaction of phenyl acetylenes [Ph-C≡C-R, where R = C(O)CCl<sub>3</sub>, C(O)CHCl<sub>2</sub>, C(OH)<sub>2</sub>CF<sub>3</sub>, CCl<sub>3</sub> and 3-methylisoxazolo-5-carbonyl] with 5-hydroxy-5-trichloromethyl-4,5-dihydroisoxazole-3-methylene azide is reported, in moderate to good yields (67-80%). From the reaction of a 4-trichloroacetyltriazole derivative with methanol or methylamine it was possible to obtain the corresponding ester and amide derivatives, respectively, by substitution of the trichloromethyl group.

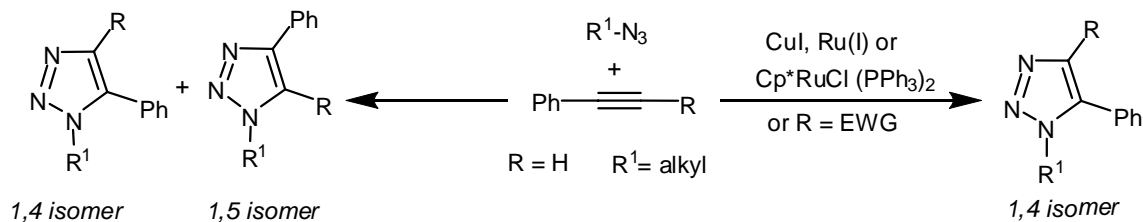
**Keywords:** 1,2,3-Triazoles, cycloadditions, azides, trihalomethyl compounds

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## Introduction

1,2,3-Triazoles are nitrogen heteroarenes which have a range of important applications in the pharmaceutical and agricultural industries<sup>1</sup> The most widely used method for the synthesis of 1,2,3-triazoles, pioneered by Huisgen, involves the thermal 1,3-dipolar cycloaddition of organic azides with alkynes.<sup>2</sup> The 1,3-dipolar cycloaddition of azides to alkynes is a versatile route to obtain 1,2,3-triazoles,<sup>3</sup> the progress in this area has been reviewed periodically.<sup>4</sup> The main challenge associated to this reaction is a regioisomeric mixture of products when unsymmetrical alkynes are used. Recently, the so-called 'click chemistry', establishing heteroatom linkages

between unsaturated building blocks, has become probably the most effective way to connect such molecules.<sup>5</sup> Among them, the CuI-catalyzed version<sup>6</sup> of the Huisgen [3 + 2]-cycloaddition<sup>7</sup> between a terminal alkyne and an azide is to date the most practical and useful 'click reaction', regioselectively affording 1,4-disubstituted 1,2,3-triazoles (Scheme 1).<sup>8</sup> More recently,<sup>9</sup> it was demonstrated that the reaction of terminal alkynes with alkyl azides is also catalyzed by Cp\*RuCl(PPh<sub>3</sub>)<sub>2</sub> in refluxing benzene, resulting in only one product for most substrates (Scheme 1). In addition, the combination of substituents on the azide<sup>10</sup> and the alkyne allows the preparation of diverse N-substituted 1,2,3-triazoles.<sup>11</sup> The cycloaddition reactions of alkynes containing substituents such as esters<sup>10b</sup> carboxyl, hydroxyl, keto, aryl, haloalkyl, trimethylsilyl, phenylsulfonyl, or phosphonate groups,<sup>12</sup> and azides containing metal acetylides,<sup>13</sup> alkynic Grignard reagents,<sup>14</sup> and phosphonium salts<sup>15</sup> have been used and it has been demonstrated that is possible to obtain some regioselectivity (Scheme 1).



### Scheme 1

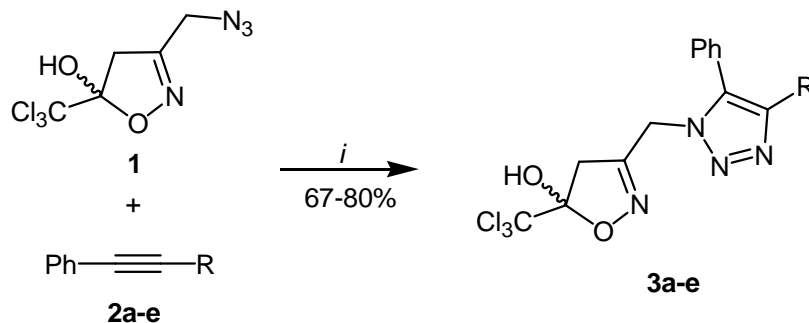
In connection with our ongoing programme on the synthesis of trihalomethyl compounds<sup>16</sup> we were interested in exploring the above cycloaddition reaction where some of the key building blocks contained halomethyl groups. To the best of our knowledge, there are no examples of 1,3-dipolar cycloadditions of heterocyclic methylene azides with halomethyl- or halomethylcarbonyl-substituted alkynes and, accordingly, the aim of this work was to explore the influence of these alkyne substituents on the regiochemistry of 1,3-cycloaddition reactions leading to the corresponding 1,2,3-triazoles.

## Results and Discussion

Herein, we report a mild and efficient synthetic approach for the preparation of a series of 4-substituted-1-(5- Trichloromethyl -5-hydroxy-4,5-dihydroisoxazole-3-methylene)-5-phenyl-1*H*-1,2,3-triazoles **3a-e** in moderate to good yields, from the cycloaddition reaction of 3-azidomethyl-5-hydroxy-5-trichloromethyl-4,5-dihydro isoxazole (**1**) with four haloacetylenes **2a-d** and one 3-methyl isoxazole acetylene **2e** (Scheme 2). Compound **1** was obtained from the cyclocondensation reaction of 5-azido-1,1,1-trichloro-4-methoxy-3-penten-2-one with hydroxylamine hydrochloride and pyridine at a molar ratio of 1:1.2:1.2, respectively, in methanol at reflux for 16h.<sup>17</sup> The synthesis of compounds **2a-e** was carried out from the reaction of lithium

acetylenide with the corresponding electrophilic agent ( $\text{CCl}_3\text{COCl}$ ,  $\text{CHCl}_2\text{COCl}$ ,  $(\text{CF}_3\text{CO})_2\text{O}$ ,  $\text{HCCl}_3$ , and 3-methylisoxazolo-5-carbonyl chloride) in the presence of boron trifluoride diethyl etherate.<sup>18</sup>

The cycloaddition reactions of **1** with **2a-e** to afford **3a-d** were carried out in toluene at  $110^\circ\text{C}$  for 36-52h. In the synthesis of **3e**, under the same conditions, we obtained only starting materials. To prepare compound **3e**, the best method was to use acetonitrile as solvent at  $80^\circ\text{C}$  for 52h. Under these conditions we were able to obtain 1,2,3-triazoles **3a-e** regioselectively.



2, 3	R	Yield of 3 (%)
<b>a</b>	$\text{C}(\text{O})\text{CCl}_3$	80
<b>b</b>	$\text{C}(\text{O})\text{CHCl}_2$	78
<b>c</b>	$\text{C}(\text{OH})_2\text{CF}_3$	70
<b>d</b>	$\text{CCl}_3$	75
<b>e</b>	3-methylisoxazolo-5-carbonyl	67

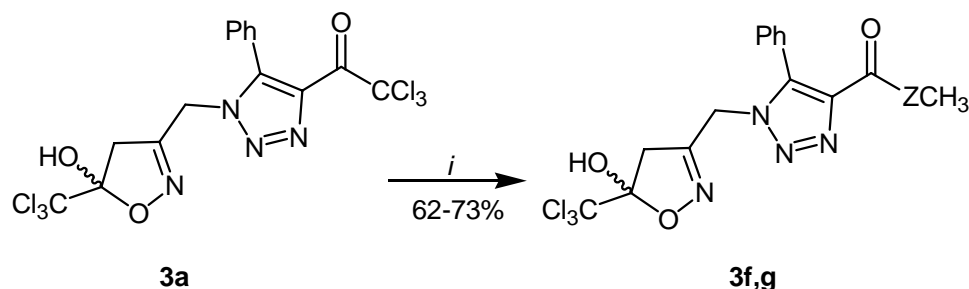
*i*: toluene,  $110^\circ\text{C}$ , 36 - 48 h (**3a-d**);

*i*: acetonitrile,  $80^\circ\text{C}$ , 52h (**3e**).

## Scheme 2

In all the cases the cycloadditions were totally regioselective, affording only triazole *1,4*-isomer. Although the *1,4*- isomers predominate, presumably for polarity reasons, the regiochemistry of the products could appear from the  $^1\text{H-NMR}$  spectra where the  $\text{N-CH}_2$  groups resonate in the range 5.43-5.53 ppm, characteristic of *1,4*-isomers. In contrast, *1,5* isomers resonate in the range 5.62-5.65 ppm<sup>[9]</sup>. The spectral  $^1\text{H NMR}$  data of the triazoles synthesized by us, presented chemical shift of the methylene group are in the range of 4.12-5.20 ppm indicate that the compound isolated are the *1,4*- isomer. The IR spectral data for the *1,4*-triazoles presented a range of OH stretching group at  $3400\text{-}3440\text{ cm}^{-1}$  for all the compounds. In addition, compound **3f** displayed an amide stretching absorption at  $3225\text{ cm}^{-1}$  while compound **3g** showed an ester stretching absorption at  $2100\text{ cm}^{-1}$ . Compounds **3a,b** and **e** gave a  $\text{C}=\text{O}$  stretching

absorption in the range 1705-1731  $\text{cm}^{-1}$ . All triazoles displayed a C-H stretching absorption in the 1214-1673  $\text{cm}^{-1}$  range and a C-halogen stretching absorption in the 667-806  $\text{cm}^{-1}$  range. The classical cycloaddition of phenylacetylene with benzyl azide without any catalyst, does not take place in toluene at room temperature,<sup>19</sup> or leads to a 1:1 mixture of regioisomers after a prolonged reaction time at reflux.<sup>19</sup> In addition, it is known that alkynes with an electron-withdrawing functional group favor the irreversible Huisgen cycloaddition reaction of azides and alkynes.<sup>20</sup> It was also recently reported that it is possible to impart some regioselectivity into these thermal cycloaddition reactions by utilizing sterically or electronically biased alkynes.<sup>21</sup> In the present work, the synthesis of five 1,2,3-triazoles from the reaction of azide and substituted-alkyne blocks containing electron-withdrawing groups with differences in the degree of electronic effect was presented. In all cases, the method reported affords the 4-substituted-1-(5-trichloromethyl-5-hydroxy-4,5-dihydroisoxazole-3-methylene)-5-phenyl-1*H*-1,2,3-triazole isomer, highly regioselective, in moderate to good yields (67-80%). The scope of this work was not limited to the synthesis of 1,2,3-triazoles from the cycloaddition of azides and halomethylated acetylenes, but it was derivate of these compounds. Thus, with the objective of showing the importance of a trichloromethyl group as a good leaving-group for carbonyl nucleophilic substitution, compound **3a** was used as substrate to obtain **3f**, **3g**. The synthesis of compound **3f** was carried out from the reaction of methylamine in acetonitrile at reflux for 24h, in the presence of boron trifluoride etherate, whereas, compound **3g** was prepared by the reaction of sodium methoxide in methanol at reflux for 24h (**Scheme 3**).



Z = NH, O

*i*: MeNH<sub>2</sub>, acetonitrile, BF<sub>3</sub>•Et<sub>2</sub>O, reflux 24h (**3f**, yield: 62%);

*i*: MeOH / MeONa, reflux, 24h (**3g**, yield: 73%).

### Scheme 3

### Conclusions

In conclusion, we have reported *for the first time* the use of halomethylated alkynes in azide alkyne cycloaddition reaction, without any catalysts. We have developed a simple and efficient

method for the [3 + 2]-cycloaddition of halomethylated alkynes with azides to obtain a single regioisomer of the 4-substituted 1,2,3-triazoles. Thus, we have successfully demonstrated the applications of 1,3-dipolar cycloaddition reactions on azido-alkynes of trihalomethylated compounds, which provided several interesting products based on the linkage between the alkyne and azido functionalities.

## Experimental Section

**General Procedures.** Unless otherwise indicated, all common solvents were used as obtained from commercial suppliers without further purification. Yields listed in Table 1 are of isolated compounds.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker DPX 200 spectrometer ( $^1\text{H}$  at 200.13 MHz and  $^{13}\text{C}$  at 50.32 MHz) and Bruker DPX 400 spectrometer, ( $^1\text{H}$  at 400.13 MHz and  $^{13}\text{C}$  at 100.63 MHz), 298K, digital resolution of  $\Gamma$  0.01 ppm, 0.1 M in  $\text{CDCl}_3$  containing TMS as internal standard. All spectra were acquired in a 5 mm tube, at natural abundance.

### Preparation of 1,2,3-triazoles 3a-d

To a solution of compound **1** (5 mmol) in toluene (15 mL), a solution of haloacetylene **2a-d** (5 mmol) in toluene (5 mL) was added. The mixture was stirred for 36-48h at 110°C (see Table 1). After this, the mixture was washed with distilled water (3  $\times$  30 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  20 mL). The organic phase was dried with  $\text{MgSO}_4$  and the solvent was removed under reduced pressure. The residue was purified by column chromatography over Merck silica gel, using a 10:1 mixture of hexane/ethyl acetate or by recrystallization using cyclohexane as eluent.

**4-Trichloroacetyl-5-phenyl-1-(5-trichloromethyl-5-hydroxy-4,5-dihydroisoxazole-3-methylene)-1H-1,2,3-triazole (3a).** Yield: 4.0 mmol (80%);  $\text{C}_{15}\text{H}_{10}\text{Cl}_6\text{N}_4\text{O}_3$ ; m.w. 506.98; mp 148-150 °C. IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ) 3400, 1725, 1235, 741.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  (*J*, Hz), 7.58-7.26 (m, 5 H, Ph), 5.27 (dd, 2 H, H-6), 3.71 (d, 1 H, *J* = 20, H-4a), 3.33 (d, 1 H, *J* = 20, H-4b).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$ , 174.3 (C-12), 153.8 (C-3), 145.1 (C-11), 136.6 (C-10), 131.2-129.5-129.5-124.0 (Ph), 111.9 (C-5), 100.2 ( $\text{CCl}_3$ ), 94.7 (C-13), 45.1 (C-6), 44.4 (C-4). MS: *m/z* (%) 504 ( $\text{M}^+$ , 5), 426 (20), 175 (58), 117 (15), 77 (14). Anal.calcd: C,35.54; H, 1.99; N, 11.02. Found: C, 35.44; H, 1.98; N, 11.02.

**4-Dichloroacetyl-5-phenyl-1-(5-trichloromethyl-5-Hydroxy-4,5-dihydroisoxazole-3-methylene)-1H-1,2,3-triazole (3b).** Yield: 3.9 mmol (78%);  $\text{C}_{15}\text{H}_{11}\text{Cl}_5\text{N}_4\text{O}_3$ ; m.w. 472.53; oil. IR ( $\nu$ ,  $\text{cm}^{-1}$ ) 3430, 1731, 1625, 1214, 1460, 699.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  (*J*, Hz), 7.49-7.39 (m, 5H, Ph), 5.20 (s, 2 H, H-6), 3.58 (d, 1 H, *J* = 18, H-4a), 3.22 (d, 1 H, *J* = 18, H-4b).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$ , 179.7 (C-12), 155.6 (C-3), 153.9 (C-10), 143.1 (C-11), 131.3-129.6-129.2-123.5(Ph), 111.7 (C-5), 100.3 ( $\text{CCl}_3$ ), 67.2 (C-13), 46.9 (C-6), 44.3 (C-4). MS: *m/z* (%) 470 ( $\text{M}^+$ , 25), 391 (21), 165 (60), 111 (8), 117 (13), 77 (18). Anal.calcd: C,38.13; H, 2.35; N, 11.86. Found: C, 37.95; H, 2.34; N, 11.80.

**4-[2-(1,1,1-Trifluoroethano-2,2-diol)]-5-phenyl-1-(5-trichloromethyl-5-hydroxy-4,5-diidroisoxazole-3-methylene)-1H-1,2,3-triazole (3c).** Yield: 3.5 mmol (70%);  $C_{15}H_{12}Cl_3F_3N_4O_4$ ; m.w. 475.64; oil. IR ( $\nu$ ,  $cm^{-1}$ ) 3434, 1459, 1235, 785, 689.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  ( $J$ , Hz), 7.61-7.44 (m, 5 H, Ph), 4.16 (dd, 1 H, H-6), 3.74 (d, 1 H,  $J = 18$ , H-4a), 3.32 (d, 1 H,  $J = 18$ , H-4b).  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  ( $J_{C-F}$ , Hz), 139.8 (C-3), 132.1 (C-10), 132.3-123-7 (Ph), 128.8 (q,  $^1J = 270$ ,  $CF_3$ ), 127.8 (C-11), 111.9 (C-5), 100.47 ( $CCl_3$ ), 72.1 (q,  $^2J = 35$ ), 46.9 (C-6), 44.7 (C-4). MS: m/z (%) 474 ( $M^+$ , 2), 396 (13), 298 (20), 175 (11), 77 (21). Anal.calcd: C, 37.88; H, 2.54; N, 11.78. Found: C, 37.80; H, 2.55; N, 11.75.

**4-Trichloromethyl-5-phenyl-1-(5-trichloromethyl-5-hydroxy-4,5-dihydroisoxazole-3-methylene)-1H-1,2,3-triazole (3d).** Yield: 3.75 mmol (75%);  $C_{14}H_{10}Cl_6N_4O_2$ ; m.w. 478.97; oil. IR ( $\nu$ ,  $cm^{-1}$ ) 3440, 1224, 667.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  ( $J$ , Hz), 7.40-7.16 (m, 5 H, Ph), 4.12 (s, 1 H, H-6), 3.72 (d, 1 H,  $J = 22$ , H-4a), 3.28 (d, 1 H,  $J = 22$ , H-4b).  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$ , 155.7 (C-3), 137.7 (C-10), 131.9 (C-11), 128.9-128.0 (Ph), 119.3 (C-3), 111.5 (C-5), 100.5 ( $CCl_3$ ), 90.1 (C-12,  $CCl_3$ ), 46.8 (C-6), 44.3 (C-4). MS: m/z (%) 476 ( $M^+$ , 8), 398 (18), 175 (54), 115 (14), 77 (17), 69 (6). Anal.calcd: C, 35.11; H, 2.10; N, 11.70. Found: C, 34.94; H, 2.09; N, 11.64.

### Compound 1,2,3-triazoles 3e

To a solution of compound **1** (5 mmol) in acetonitrile (15 mL) was added a solution of isoxazole acetylene **2e** (5 mmol) in acetonitrile (5 mL). The mixture was stirred for 52h at 80°C. After this, the mixture was washed with distilled water (3 × 30 mL) and extracted with  $CH_2Cl_2$  (3 × 20 mL). The organic phase was dried with  $MgSO_4$  and the solvent was removed under reduced pressure. The residue was purified by column chromatography over Merck silica gel, using a 10:1 mixture of hexane/ethyl acetate as eluent.

**4-(3-Methyl-5-carbonilisoxazol)-5-phenyl-1-(5-trichloromethyl-5-hydroxy-4,5-diidroisoxazole-3-methylene)-1H-1,2,3-triazole (3e).** Yield: 2.85 mmol (57 %);  $C_{18}H_{14}Cl_3N_5O_4$ ; m.w. 470.68; oil. IR ( $\nu$ ,  $cm^{-1}$ ) 3430, 1673, 1705, 697.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  ( $J$ , Hz), 7.61-7.44 (m, 5 H, Ph), 6.80 (s, 1 H, H-17), 4.16 (s, 2 H, H-6), 3.74 (d, 1 H,  $J = 18$ , H-4a), 3.35 (d, 1 H,  $J = 18$  Hz, H-4b), 2.17 ( $CH_3$ ).  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$ , 172.0 (C-12), 160.4 (C-3), 155.6 (C-16), 134.4 (C-10), 133.2 (C-11), 128.2 (Ph), 11.5 (C-17), 109.9 (C-5), 100.5 ( $CCl_3$ ), 46.8 (C-6), 44.3 (C-4), 11.2 ( $CH_3$ ). MS: m/z (%) 469 ( $M^+$ , 5), 387 (10), 293 (11), 175 (33), 117 (8), 82 (40), 77 (25). Anal.calcd: C, 45.93; H, 3.00; N, 14.88. Found: C, 45.82; H, 2.99; N, 14.84.

### Compound 1,2,3-triazole 3f

To a solution of compound **3a** (5mmol) in acetonitrile (10mL), was added 1 eq. of  $BF_3 \cdot Et_2O$  (0,63mL) followed by methylamine (7mmol). The mixture was stirred for 24h at 80 °C. After this, the solvent was removed under reduced pressure and extracted using a procedure analogous to that with **3e**, except that the product was not purified by column chromatography.

**1-(5-Trichloromethyl-5-hydroxy-4,5-dihydroisoxazol-3-methylene)-5-phenyl-1H-1,2,3-triazol-4-N-methylcarboxamide (3f).** Yield: 3.1mmol (62%);  $C_{15}H_{14}Cl_3N_5O_3$ ; m.w. 418.67; oil.

IR ( $\nu$ ,  $\text{cm}^{-1}$ ) 3440, 3225, 1642, 1470, 1230, 712.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  ( $J$ , Hz), 7.51-7.42 (m, 5 H, Ph), 5.18 (s, 2 H, H-6), 3.58 (d, 1 H,  $J = 20$ , H-4a), 3.23 (d, 1 H,  $J = 20$ , H-4b), 3.63 (s, 3 H,  $\text{NHCH}_3$ ).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$ , 159.7 (C-12), 155.5 (C-3), 131.9 (C-11), 131.8 (C-10), 129.3-128.88-128.3-121.2 (Ph), 11.5 (C-5), 102.4 ( $\text{CCl}_3$ ), 44.1 (C-6), 41.3 (C-4), 26.2 ( $\text{NHCH}_3$ ). MS:  $m/z$  (%) 417 ( $\text{M}^+$ , 3), 358 (15), 325 (10), 227 (11), 175 (33), 77 (17), 44 (40). Anal.calcd: C, 43.03; H, 3.37; N, 16.73. Found: C, 42.85; H, 3.36; N, 16.66.

### Compound 1,2,3-triazol 3g

To a solution of compound **3a** (5mmol) in methanol (10mL) was added sodium methoxide (5mmol) and the mixture was stirred for 24h at 65°C. After this, the solvent was removed under reduced pressure and extracted using an analogous procedure to that with **3e**. The product was purified by recrystallization in cyclohexane/ chloroform 90/10.

**1-(5-Tricholomethyl-5-hydroxy-4,5-diidroisoxazol-3-methylene)-5-phenyl-1H-1,2,3,-triazol-4-N-Methylcarboxilate (3g)**. Yield: 3.65 mmol (73%);  $\text{C}_{15}\text{H}_{13}\text{Cl}_3\text{N}_4\text{O}_4$ ; m.w. 419.65; mp 63-65 °C. IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ) 3407, 2107, 1717, 806, 698.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  ( $J$ , Hz), 7.45-7.40 (m, 5 H, Ph), 5.28 (dd, 2H, H-6), 3.63 (s, 3 H,  $\text{OCH}_3$ ), 3.54 (d, 1 H,  $J = 20$ , H-4a), 3.20 (d, 1 H,  $J = 20$ , H-4b).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$ , 174.3 (C-12), 160.9 (C-3), 154.2 (C-11), 145.3 (C-10), 131.1-129.7-129.1-128.9 (Ph), 112.1 (C-5), 100.3 ( $\text{CCl}_3$ ), 52.1 ( $\text{OCH}_3$ ), 45.1 (C-6), 44.4 (C-4). MS:  $m/z$  (%) 418 ( $\text{M}^+$ , 4), 358 (15), 175 (27), 77 (16), 242 (9), 77 (14). Anal.calcd: C, 42.93; H, 3.12; N, 13.35. Found: C, 42.80; H, 3.11; N, 13.31.

### Acknowledgements

The authors thank the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Fundação de Amparo a Pesquisa do Rio Grande do Sul (FAPERGS) for financial support and fellowships.

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