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

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Dedicated to Prof. Oleg Kulinkovich on the occasion of his 60th birthday

Abstract
A convenient method to obtain a series of 1-(5-hydroxy-5-trichloromethyl-4,5-dihydroisoxazole-3-methylene)-5-phenyl-1H-1,2,3-triazoles by a regiospecific cycloaddition reaction of phenyl acetylenes [Ph–C≡C–R, where R = C(O)CCl3, C(O)CHCl2, C(OH)2CF3, CCl3 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

Introduction
1,2,3- Triazoles are nitrogen heteroarenes which have a range of important applications in the pharmaceutical and agricultural industries.1 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.2 The 1,3-dipolar cycloaddition of azides to alkynes is a versatile route to obtain 1,2,3-triazoles,3 the progress in this area has been reviewed periodically.4 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. Among them, the CuI-catalyzed version of the Huisgen [3 + 2]-cycloaddition 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). More recently, it was demonstrated that the reaction of terminal alkynes with alkyl azides is also catalyzed by Cp*RuCl(PPh3)2 in refluxing benzene, resulting in only one product for most substrates (Scheme 1). In addition, the combination of substituents on the azide and the alkyne allows the preparation of diverse N-substituted 1,2,3-triazoles. The cycloaddition reactions of alkynes containing substituents such as esters, carboxyl, hydroxyl, keto, aryl, haloalkyl, trimethylsilyl, phenylsulfonyl, or phosphonate groups; and azides containing metal acetylides, alkynic Grignard reagents, and phosphonium salts have been used and it has been demonstrated that it is possible to obtain some regioselectivity (Scheme 1).

Scheme 1

In connection with our ongoing programme on the synthesis of trihalomethyl compounds 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-1H-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. The synthesis of compounds 2a-e was carried out from the reaction of lithium
acetylenide with the corresponding electrophilic agent (CCl₃COCl, CHCl₂COCl, (CF₃CO)₂O, HCCl₃, and 3-methylisoxazolo-5-carbonyl chloride) in the presence of boron trifluoride diethyl etherate.¹⁸

The cycloaddition reactions of 1 with 2a-e to afford 3a-d were carried out in toluene at 110°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°C for 52h. Under these conditions we were able to obtain 1,2,3-triazoles 3a-e regiospecifically.

\[
\text{1} + \text{2a-e} \rightarrow \text{3a-e} \quad \text{Yield of 3a-e: 67-80\%}
\]

<table>
<thead>
<tr>
<th>2, 3</th>
<th>R</th>
<th>Yield of 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>C(O)CCl₃</td>
<td>80</td>
</tr>
<tr>
<td>b</td>
<td>C(O)CHCl₂</td>
<td>78</td>
</tr>
<tr>
<td>c</td>
<td>C(OH)₂CF₃</td>
<td>70</td>
</tr>
<tr>
<td>d</td>
<td>CCl₃</td>
<td>75</td>
</tr>
<tr>
<td>e</td>
<td>3-methylisoxazolo-5-carbonyl</td>
<td>67</td>
</tr>
</tbody>
</table>

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

\[i: \text{acetonitrile, } 80^\circ\text{C, } 52\text{h (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 ¹H-NMR spectra where the N-CH₂ 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[^9]. The spectral ¹H 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 3400-3440 cm⁻¹ for all the compounds. In addition, compound 3f displayed an amide stretching absorption at 3225 cm⁻¹ while compound 3g showed an ester stretching absorption at 2100 cm⁻¹. Compounds 3a,b and e gave a C=O stretching
absorption in the range 1705-1731 cm\(^{-1}\). All triazoles displayed a C-H stretching absorption in the 1214-1673 cm\(^{-1}\) range and a C-halogen stretching absorption in the 667-806 cm\(^{-1}\) range. The classical cycloaddition of phenylacetylene with benzyl azide without any catalyst, does not take place in toluene at room temperature,\(^{19}\) or leads to a 1:1 mixture of regioisomers after a prolonged reaction time at reflux.\(^{19}\) In addition, it is known that alkynes with an electron-withdrawing functional group favor the irreversible Huisgen cycloaddition reaction of azides and alkynes.\(^{20}\) 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.\(^{21}\) 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).

\[
\begin{align*}
\text{3a} & \xrightarrow[i]{MeNH_2, \text{acetonitrile, BF}_3\cdot\text{Et}_2\text{O, reflux 24h (3f, yield: 62%)}} \quad \text{3f, g} \\
& \xrightarrow[i]{MeOH / \text{MeONa, reflux, 24h (3g, yield: 73%)}}
\end{align*}
\]

\text{Z} = \text{NH, O}

\text{Scheme 3}

Conclusions

In conclusion, we have reported for the first time the use of halomethylated alkynes in azide alkynes 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. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker DPX 200 spectrometer ($^1$H at 200.13 MHz and $^{13}$C at 50.32 MHz) and Bruker DPX 400 spectrometer, ($^1$H at 400.13 MHz and $^{13}$C at 100.63 MHz), 298K, digital resolution of $\Gamma$ 0.01 ppm, 0.1 M in 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 x 30 mL) and extracted with CH$_2$Cl$_2$ (3 x 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 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%); C$_{15}$H$_{10}$Cl$_6$N$_4$O$_3$; m.w. 506.98; mp 148-150 ºC. IR (KBr, v, cm$^{-1}$) 3400, 1725, 1235, 741. $^1$H NMR (400 MHz, 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). $^{13}$C NMR (100 MHZ, 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 (CCl$_3$), 94.7 (C-13), 45.1 (C-6), 44.4 (C-4). MS: m/z (%) 504 (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%); C$_{15}$H$_{11}$Cl$_5$N$_4$O$_3$; m.w. 472.53; oil. IR (v, cm$^{-1}$) 3430, 1731, 1625, 1214, 1460, 699. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (J, Hz), 7.49-7.39 (m, 5 H, Ph), 5.20 (s, 2 H, H-6), 3.71 (d, 1 H, $J$ = 20, H-4a), 3.33 (d, 1 H, $J$ = 20, H-4b). $^{13}$C NMR (100 MHZ, 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 (CCl$_3$), 94.7 (C-13), 45.1 (C-6), 44.4 (C-4). MS: m/z (%) 470 (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-diidoisoxazole-3-methylene)-1H-1,2,3-triazole (3e). Yield: 3.5 mmol (70%); C_{15}H_{12}Cl_{3}F_{3}N_{4}O_{4}; m.w. 475.64; oil. IR (v, cm^{-1}) 3434, 1549, 1235, 785, 689. ^1H NMR (400 MHz, CDCl_{3}): δ (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). ^13C NMR (100 MHz, CDCl_{3}): δ (J_{C-F}, Hz), 139.8 (C-3), 132.1 (C-10), 132.4-123-7 (Ph), 128.8 (q, ^2J_{C-F} = 270, CF_{3}), 127.8 (C-11), 111.9 (C-5), 100.47 (CCl_{3}), 72.1 (q, ^2J_{C-F} = 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_{6}N_{4}O_{2}; m.w. 478.97; oil. IR (v, cm^{-1}) 3440, 1224, 667. ^1H NMR (400 MHz, CDCl_{3}): δ (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). ^13C NMR (100 MHz, CDCl_{3}): δ, 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_{2}Cl_{2} (3 x 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-diidoisoxazole-3-methylene)-1H-1,2,3-triazole (3e). Yield: 2.85 mmol (57 %); C_{18}H_{14}Cl_{3}N_{5}O_{4}; m.w. 470.68; oil. IR (v, cm^{-1}) 3430, 1673, 1705, 697. ^1H NMR (400 MHz, CDCl_{3}): δ (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}). ^13C NMR (100 MHz, CDCl_{3}): δ, 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}•Et_{2}O (0.63mL) followed by methyamine (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_{3}N_{5}O_{3}; m.w. 418.67; oil.
IR (ν, cm⁻¹) 3440, 3225, 1642, 1470, 1230, 712. ¹H NMR (400 MHz, CDCl₃): δ (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, NHCH₃). ¹³C NMR (100 MHz, CDCl₃): δ, 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 (CCl₃), 44.1 (C-6), 41.3 (C-4), 26.2 (NHCH₃). MS: m/z (%) 417 (M⁺, 3), 358 (15), 325 (10), 227 (11), 175 (33), 77 (17), 44 (40). Anal.calcd: C, 42.85; H, 3.36; N, 16.66.

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

To a solution of compound 3a (5 mmol) in methanol (10 mL) was added sodium methoxide (5 mmol) 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-Trichloromethyl-5-hydroxy-4,5-dihydroisoxazol-3-methylene)-5-phenyl-1H-1,2,3-triazol-4-N-Methylcarboxilate (3g). Yield: 3.65 mmol (73%); C₁₅H₁₃Cl₃N₄O₄; m.w. 419.65; mp 63-65 °C. IR (KBr, ν, cm⁻¹) 3407, 2107, 1717, 806, 698. ¹H NMR (400 MHz, CDCl₃): δ (J, Hz), 7.45-7.40 (m, 5 H, Ph), 5.28 (dd, 2H, H-6), 3.63 (s, 3 H, OCH₃), 3.54 (d, 1 H, J = 20, H-4a), 3.20 (d, 1 H, J = 20, H-4b). ¹³C NMR (100 MHz, CDCl₃): δ, 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 (CCl₃), 52.1 (OCH₃), 45.1 (C-6), 44.4 (C-4). MS: m/z (%) 418 (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.

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