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,*[a] Daniel J. Emmerich,[b] Adilson P. Sinhorin,[c] Marcelo Rossatto,[a] Clarissa P. Frizzo,[a] Helio G. Bonacorso,[a] and Nilo Zanata[a]

[a] *Núcleo de Química de Heterociclos (NUQUIMHE), Departamento de Química, Universidade Federal de Santa Maria, 97105-900, Santa Maria, RS, Brasil*
[b] *Departamento de Química, Universidade Regional Integrada do Alto Uruguai e das Missões, Erechim, RS, Brasil; Departamento de Química, [c]Universidade Federal do Mato Grosso, Sinope, MT, Brasil*
E-mail: mmartins@base.ufsm.br

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

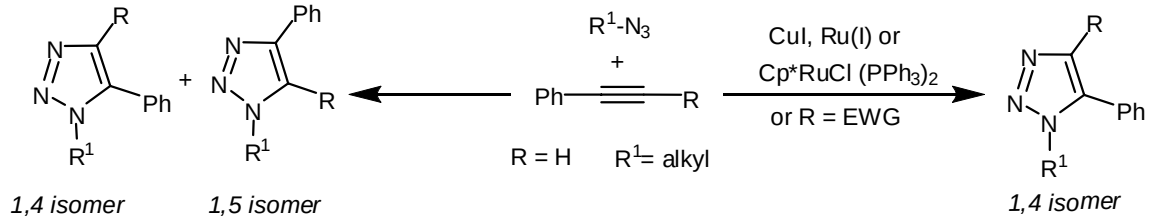
Abstract
A convenient method to obtain a series of 1-(5-hydroxy-5-trichloromethyl-4,5-dihydroisoxazole-3-methylene)-5-phenyl-1*H*-1,2,3-triazoles by a regiospecific cycloaddition reaction of phenyl acetylenes [Ph–C≡C–R, where R = $C(O)CCl_3$, $C(O)CHCl_2$, $C(OH)_2CF_3$, CCl_3 and 3-methylisoxazolo-5-carbonyl] 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.[5] Among them, the CuI-catalyzed version[6] of the Huisgen [3 + 2]-cycloaddition[7] 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).[8] More recently,[9] it was demonstrated that the reaction of terminal alkynes with alkyl azides is also catalyzed by $Cp^*RuCl(PPh_3)_2$ in refluxing benzene, resulting in only one product for most substrates (Scheme 1). In addition, the combination of substituents on the azide[10]and the alkyne allows the preparation of diverse N-substituted 1,2,3-triazoles.[11] The cycloaddition reactions of alkynes containing substituents such as esters[10b] carboxyl, hydroxyl, keto, aryl, haloalkyl, trimethylsilyl, phenylsulfonyl, or phosphonate groups;[12] and azides containing metal acetylides,[13] alkynic Grignard reagents,[14] and phosphonium salts[15] have been used and it has been demonstrated that is possible to obtain some regioselectivity (Scheme 1).



Scheme 1

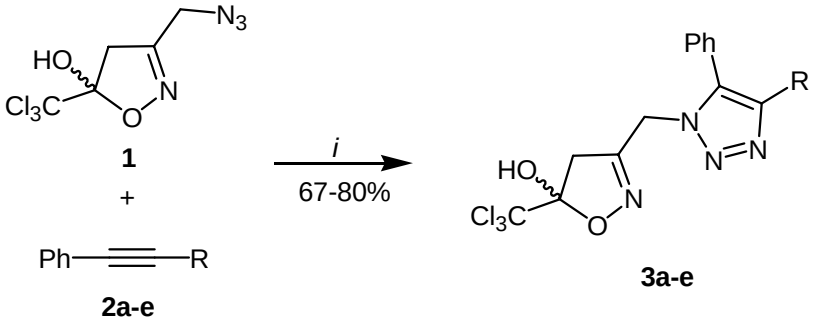
In connection with our ongoing programme on the synthesis of trihalomethyl compounds[16] we were interested in exploring the above cycloaddition reaction where some of the key building blocks contained halomethyl groups. To the best of our knowledge, there are no examples of 1,3-dipolar cycloadditions 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.[17] The synthesis of compounds **2a-e** was carried out from the reaction of lithium

acetylenide with the corresponding electrophilic agent (CCl_3COCl, $CHCl_2COCl$, $(CF_3CO)_2O$, $HCCl_3$, 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.



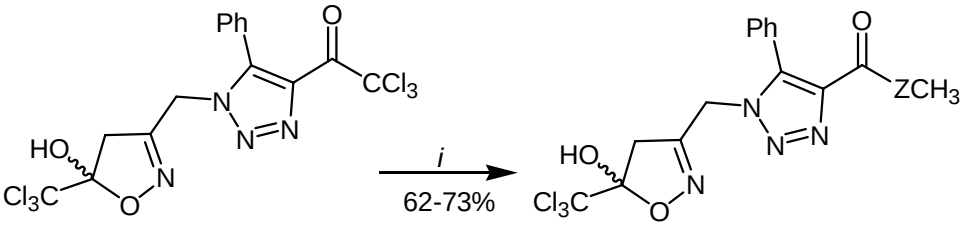
2, 3	R	Yield of **3** (%)
a	$C(O)CCl_3$	80
b	$C(O)CHCl_2$	78
c	$C(OH)_2CF_3$	70
d	CCl_3	75
e	3-methylisoxazolo-5-carbonyl	67

i: toluene, 110°C, 36 - 48 h (**3a-d**);
i: acetonitrile, 80°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}H-NMR spectra where the 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[9]. The spectral ^{1}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 3400-3440 cm^{-1} for all the compounds. In addition, compound **3f** displayed an amide strething absorption at 3225 cm^{-1} while compound **3g** showed an ester stretching absortion 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 regiosselective, 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**).



3a **3f,g**

Z = NH, O

i: $MeNH_2$, acetonitrile, $BF_3 \bullet Et_2O$, 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 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 Γ 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^{o}C (see Table 1). 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 or by recrystallization using cyclohexane as eluent.

4-Trichloroacetyl-5-phenyl-1-(5-trichloromethyl-5-hydroxy-4,5-dihydroisoxazole-3-methylene)-1*H*-1,2,3-triazole (3a). Yield: 4.0 mmol (80%); $C_{15}H_{10}Cl_6N_4O_3$; m.w. 506.98; mp 148-150 ºC. IR (KBr, ν, cm^{-1}) 3400, 1725, 1235, 741. ^{1}H NMR (400 MHz, $CDCl_3$): δ (*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, $CDCl_3$): δ, 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)-1*H*-1,2,3-triazole (3b). Yield: 3.9 mmol (78%); $C_{15}H_{11}Cl_5N_4O_3$; m.w. 472.53; oil. IR (ν, cm^{-1}) 3430, 1731, 1625, 1214, 1460, 699. ^{1}H NMR (400 MHz, $CDCl_3$): δ (*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}C NMR (100 MHz, $CDCl_3$): δ, 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 (CCl_3), 67.2 (C-13), 46.9 (C-6), 44.3 (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-diidroisoxazole-3-methylene)-1*H*-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 (ν, cm^{-1}) 3434, 1459, 1235, 785, 689. ^{1}H 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). ^{13}C NMR (100 MHz, $CDCl_3$): δ (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)-1*H*-1,2,3-triazole (3d). Yield: 3.75 mmol (75%); $C_{14}H_{10}Cl_6N_4O_2$; m.w. 478.97; oil. IR (ν, cm^{-1}) 3440, 1224, 667. ^{1}H 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). ^{13}C 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_2Cl_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-diidroisoxazole-3-methylene)-1*H*-1,2,3-triazole (3e). Yield: 2.85 mmol (57 %); $C_{18}H_{14}Cl_3N_5O_4$; m.w. 470.68; oil. IR (ν, cm^{-1}) 3430, 1673, 1705, 697. ^{1}H 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). ^{13}C 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_2O (0,63mL) followed by methylamine (7mmol). The mixture was stirred for 24h at 80 ºC. 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-1*H*-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 (ν, cm^{-1}) 3440, 3225, 1642, 1470, 1230, 712. ^{1}H NMR (400 MHz, $CDCl_3$): 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, $NHCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): 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 (CCl_3), 44.1 (C-6), 41.3 (C-4), 26.2 ($NHCH_3$). MS: m/z (%) 417 (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 65ºC. 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-1*H*-1,2,3,-triazol-4-N-Methylcarboxilate (3g). Yield: 3.65 mmol (73%); $C_{15}H_{13}Cl_3N_4O_4$; m.w. 419.65; mp 63-65 ºC. IR (KBr, ν, cm^{-1}) 3407, 2107, 1717, 806, 698. ^{1}H NMR (400 MHz, $CDCl_3$): δ (*J*, Hz), 7.45-7.40 (m, 5 H, Ph), 5.28 (dd, 2H, H-6), 3.63 (s, 3 H, OCH_3), 3.54 (d, 1 H, *J* = 20, H-4a), 3.20 (d, 1 H, *J* = 20, H-4b). ^{13}C NMR (100 MHz, $CDCl_3$): 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 (CCl_3), 52.1 (OCH_3), 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.

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.

References

1. (a) Wamhoff, H. In *Comprehensive Heterocyclic Chemistry;* Katritzky, A. R.; Rees, C. W., Eds. Pergamon Press: New York, 1984. (b) Fan, W.-Q.; A. R. Katrizky, A. R. In *Comprehensive Heterocyclic Chemistry II*; Katrizky, A. R.; Rees, C. W.; Scriven, E. F. V. Pergamon Press: Oxford, 1996. (b) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, 127, 15998. (c) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H. Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem Soc*. **2008**, *130*, 8923. (d) Rasmussen, L. K.; Boren, B. C.; Fokin, V. V. *Org. Lett.* **2007**, *9*, 5337.

2. L'Abbe, G. *Chem. Rev.* **1969**, *69*, 345.
3. Lwowski, W. In *1,3-Dipolar Cycloaddition Chemistry*, Wiley: New York, 1984; Vol. 1.
4. Benson, F. R.; Savell, W. L. *Chem. Rev.* **1950**, 1. (b) Boyer, J. H. In *Heterocyclic Compounds*; Elderfield, R. C., Ed.; Wiley: New York, 1961. (c) Gilchrist, T. L.; Gymer, G. E. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R.; Boulton, A. J., Ed., Academic Press: New York, 1974. (d) A. Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Taylor, E. C.; Weissberger, A. Wiley-Interscience: New York, 1984. (e) Fan, W.-Q.; Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R.; Rees, Scriven, E. F. V., Pergamon Press: New York, 1996; (f) Sha, C.-K.; Mohanakrishnan, M. K. In *The Chemistry of Heterocyclic Compounds* Padwa, A.; Pearson, W. H., Eds., John Wiley: New York, 1972.
5. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004. (b) Kolb, H. B.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128.
6. Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. For a recent review, see: (c) Bock, V. D.; Hiemstra, J. H. van Maarseveen, *Eur. J. Org. Chem*. **2006**, 68.
7. Huisgen, R.; Szeimis, G.; Moebius, L. *Chem. Ber.* **1967**, *100*, 2494. (b) Huisgen, R. In *1,3-Dipolar Cycloadditional Chemistry*, Padwa, A., Ed. Wiley: New York, 1984; pp 1-176. (c) Huisgen, R. *Pure Appl. Chem.* **1989**, *61*, 613.
8. (a) Bodine, K. D.; Gin, D. Y.; Gin, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 1638. (b) Ryu, E. H.; Zhao, Y. *Org. Lett.* **2005**, *7*, 1035. (c) Dichtel, W. R.; Miljanic, O. S.; Spruell, J. M.; Health, J. R.; Stoddart, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 10388. (d) Aucagne, V.; Leigh, D. A. *Org. Lett.* **2006**, *8*, 4505.
9. Weinreb, S. M.; Majireck, M. M. *J. Org. Chem.* **2006**, *71*, 8680.
10. Sheradsky, T. In *The Chemistry of the Azido Group*, Patai, S., Ed., Interscience: New York, 1971. (b) Biagi, G.; Giorgi, I.; Livi, O.; Lucacchini, A.; Martini, C.; Scartoni, V. J. *Pharm. Sci*. **1993**, *82*, 893.
11. Padwa, A. In *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, 1991.
12. Tamura, Y.; Chun, M. W.; Kwon, S.; Bayomi, S. M.; Okada, T.; Ikeda, M. *Chem. Pharm. Bull.* **1978**, *26*, 3515. (b) Abu-Orabi, S. T.; Atfah, M. A.; Jibril, I. F. M.; Mari'i, A.; Ali, A.-S. *J. Heterocycl. Chem.* **1989**, *26*, 1461. (c) Lalezari, I.; Gomez, L. A.; Khorshidi, M. *J. Heterocycl. Chem.* **1990**, *27*, 687. (d) Gouault, N.; Cupif, J.-F.; Sauleau, A.; David, M. *Tetrahedron Lett*. **2000**, *41*, 7293.
13. Boyer, J. H.; Mack, C. H.; Goebel, N.; Morgan, L. R., Jr. *J. Org. Chem*. **1958**, *23*, 1051.
14. Akimova, G. D.; Chistokletov, V. N.; Petrov, A. A. *Zh. Org. Khim.* **1967**, *3*, 968.
15. Tanaka, Y.; Miller, S. I. *J. Org. Chem*. **1973**, *38*, 2708.
16. Martins, M. A. P.; Cunico, W.; Pereira, C. M. P.; Sinhorin, A. P.; Flores, A. F. C.; Zanatta, N. *Curr. Org. Synthesis* **2004**, *1*, 391. Martins, M. A. P.; Sinhorin, A. P.; Zimmermann, N. E. K.; Zanatta, N.; Bonacorso, H. G.; Bastos, G. P.; *Synthesis* **2001**, *13*, 1959. Bonacorso, H. G.;

Bittencourt, S. R. T.; Lourega, R. V.; Flores, A. F. C.; Zanatta, N.; Martins, M. A. P. *Synthesis* **2000**, *10*, 1431. Martins, M. A. P.; Flores, A. F. C.; Bastos, G. P.; Zanatta, N.; Bonacorso, H. G. *J. Heterocycl. Chem.* **1999**, *36*, 837.

17. Martins, M. A. P.; Emmerich, D. J.; Pereira, C. M. P.; Cunico, W.; Rossatto, M.; Zanatta, N.; Bonacorso, H. G. *Tetrahedron Lett*. **2004**, *45*, 4935.
18. Martins, M. A. P.; Sinhorin, A. P; Zimmermann, N. E. K.; Zanatta, N.; Bonacorso, H. G.; Bastos, G. P. *Synthesis* **2001**, 1959; (b) Martins, M. A. P.; Sinhorin, A. P.; Rosa, A.; Flores, A. F. C.; Wastowski, A. D.; Pereira, C. M. P.; Flores, D. C.; Beck, P.; Freitag, R. A.; Brondani, S.; Cunico, W.; Bonacorso, H. G.; Zanatta, N. *Synthesis* **2002**, 2353.
19. Chassaing, S.; Kumarraja, M.; Sani Souna Sido, A.; Pale, P.; Sommer, J. *Org. Lett.* **2007**, *9*, 883.
20. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew Chem., Int. Ed*. **2001**, *40*, 2005. (b) Palacios, F.; Retana, A. M.; Pagalday, J. *Heterocycles* **1994**, *38*, 95.
21. Hlasta, D. J.; Ackerman, J. H. *J. Org. Chem.* **1994**, *59*, 6184. (b) Coats, S. J.; Link, J. S.; Gauthier, D.; Hlasta, D. *Org. Lett.* **2005**, *7*, 1469. (c) Z. Li, Z.; Seo, T. S.; Ju, J. *Tetrahedron Lett.* **2004**, *45*, 3143.

