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Graphical Abstract

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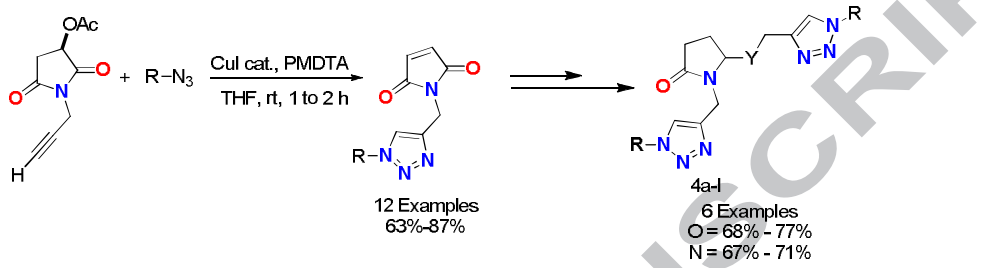

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Synthesis of Functionalized *N*-Triazolyl Maleimides

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ABSTRACT

An easy and mild two-step one-pot reaction allowed the synthesis of functionalized *N*-triazolyl maleimide. Next, the addition of propargyl alcohol and propargyl amine to the *N*-acyliminium ion mediated by Lewis acid, $In(OTf)_3$, allowed the introduction of a second 1,2,3-triazol ring at position 5 of the amide. The products in both reactions were achieved in moderate to good yields.

1. Introduction

Maleimide and its derivatives are important building blocks used as antibacterial agents,[1-4] pharmaceutical intermediates[3,5,6] (Figure 1) crosslinking reagents for natural rubbers,[7,8] resins in integrated circuit dies,[9] adhesives for fiber-reinforced composites[10] and modifiers for engineering plastics,[11] to mention a few applications.

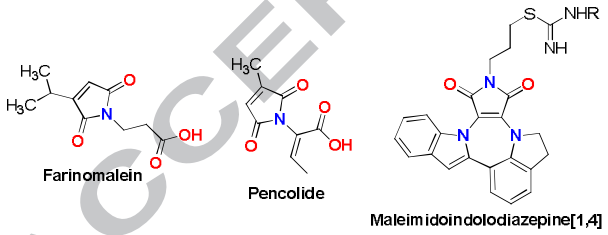


Figure 1. Biologically active maleimides

There are many approaches to synthesizing maleimide but the simplest uses maleic anhydride;[12] most papers describe functionalization of the maleimide ring and not its de novo synthesis. Hence there is a need to develop new methods to synthesize the heterocyclic ring.

N-Heterocyclic compounds are broadly distributed in nature; however, triazoles are not found in natural products.[12,13] Synthetic 1,2,3-triazoles, due to their capacity for intermolecular hydrogen bond formation, allow interactions with biological receptors[14] and find applications as agrochemical compounds,[15] corrosion inhibitors, dyes[16] and ionic liquids.[17]

The main synthetic route to 1,2,3-triazole rings is the 1,3-dipolar cycloaddition reaction,[18] which was improved in 2003 when two groups[19,13] independently introduced the use of copper salts to obtain better yields and good regioselectivity.

This kind of reaction can be performed under different conditions considered non-classical, including microwave dielectric heating, ultrasound processing, the use of ionic liquids as reaction media and continuous flow processing.[20]

N-Acyliminium ions are important intermediates that act as electron-deficient carbocations in reactions with weak nucleophiles in organic synthesis, mainly in intramolecular reactions[21] where they have found major use in the synthesis of bothe natural and unnatural nitrogen-containing products.[22,23]

This reactivity affords advantages for carbon–carbon bond formation, both in intermolecular and intramolecular processes.[23] These species have been generated from amides or lactams, which bear a good leaving group at the α-position of the nitrogen atom in acidic media.

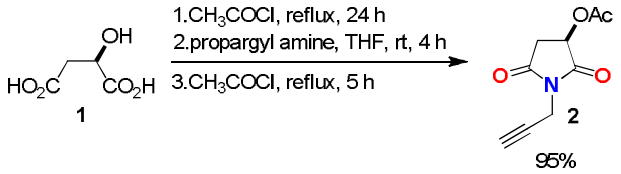
Different nucleophilic carbons react with *N*-acyliminium ions, such as allyl-, alkyl-, aryl-, and alkynylmetals, cyanotrimethylsilane (TMSCN), isonitriles, enol derivatives, and aromatics.[23]

In connection with our research interest in the preparation and reactivity of *N*-acyliminium ions,[24] we wish to report here a general procedure to access various readily available *N*-triazolyl maleimides and *N*-triazolyl-5-triazolyl pyrrolinones from the corresponding addition reaction of alcohols to the *N*-acyliminium ion mediated by $In(OTf)_3$ and further transformation in 5-triazolyl pyrrolinone.

Results and Discussion

A simple and efficient methodology to synthesize *N*-triazolyl maleimides was developed and is described here. The key step

was the synthesis of the *N*-propargyl pyrrolidone (**2**). *L*-Malic acid has proven to be a useful precursor for *N*-acyliminium ion reactions leading to enantiopure pyrrolidone derivatives (**2**).[25] The *N*-propargyl imide **2** was prepared in almost quantitative yield from inexpensive *L*-malic acid **1**, according to a procedure from the literature[26] (Scheme 1).

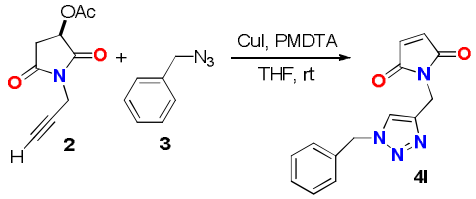


Scheme 1. Synthesis of *N*-propargyl pyrrolidone

Acid **1** was successively treated with acetyl chloride, propargyl amine and acetyl chloride to afford the respective imide **2,** generating the product in 95% yield.

With the starting material in hand, CuI was screened for optimal triazole formation conditions using benzyl azide as a model reagent in tetrahydrofuran as solvent. Representative results are presented in Table 1 (entries 1–8).

Table 1. Screening of reaction conditions for the synthesis of the *N*-1,2,3-triazole maleimide ring.



Entry	Cu mol%	PMDTA (equiv.)	Reaction Time (h)	Yield (%)
1	10	1.2	4	57
2	15	1.2	3	60
3	20	1.2	2,5	65
4	30	1.2	1	83
5	50	1.2	1	75
6	100	1.2	1	78
7	30	1.0	1	71
8	30	-	18	60[a]

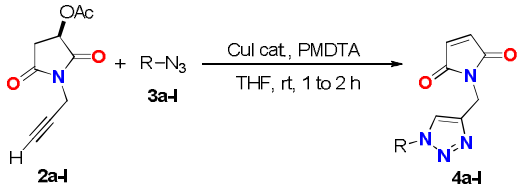
[a]The acetyl group was not eliminated

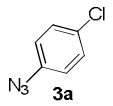
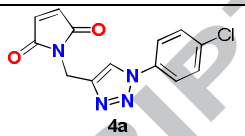
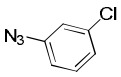
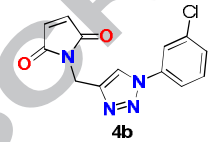
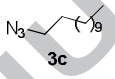
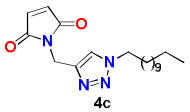
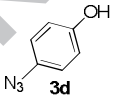
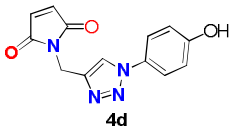
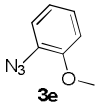
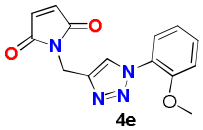
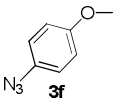
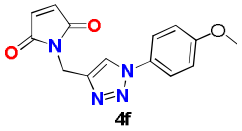
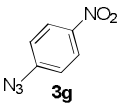
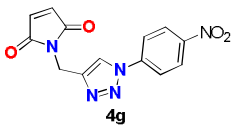
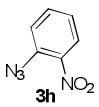
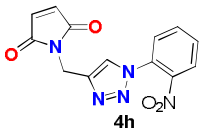
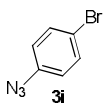
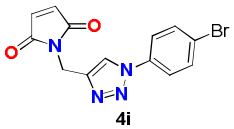
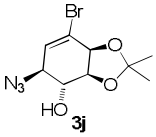
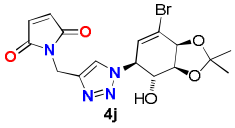
Table 1 shows us that reaction using 30 mol% CuI, *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine (PMDTA) (1.2 equiv)[27] as base and tetrahydrofuran (THF) as solvent at room temperature was the best reaction condition surveyed, leading to 83% yield of *N*-triazolyl maleimide (entry 4) in a 1 hour reaction. When the reaction was carried out in the absence of PMDTA (Table 1, entry 8) the product was still observed to form in 60% yield; however, without elimination of the acetate group.

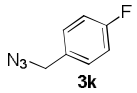
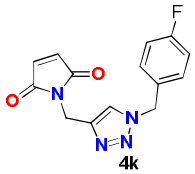
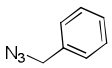
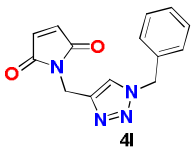
Using the conditions from Table 1, entry 4, the scope of the reaction was investigated with a variety of organic azides. As shown in Table 2, aromatic and non-aromatic organic azides were found to react smoothly with *N*-propargyl pyrrolidone to give *N*-triazolyl maleimides[28] (**4a-l**) in yields ranging from 63% to 87% (Table 2).

Table 2 shows that the presence of electron-withdrawing substituents in aromatic azides such as Cl, OH, NO_2 and Br does not seem to have a negative effect on the reaction yield, which ranged from 68% to 87% (Table 2, entries 1, 2, 4 and 7-9). The location of the electron-withdrawing substituent, whether in the *ortho*, *meta* or *para* position, did not substantially affect the yield from the reactions.

Table 2. Synthesis of *N*-triazolyl maleimides



Entry	Azide	product	Yield (%)
1	 3a	 4a	68
2	 3b	 4b	71
3	 3c	 4c	63
4	 3d	 4d	77
5	 3e	 4e	75
6	 3f	 4f	78
7	 3g	 4g	87
8	 3h	 4h	82
9	 3i	 4i	79
10	 3j	 4j	69

11	 3k	 4k	77
12	 3l	 4l	83

Aromatic azides with electron-donor substituents on the aromatic ring gave 75% and 78%, yield to methoxy group at *para* and *ortho* positions, respectively (Table 2, entries 5 and 6).

Examples derived from alkyl azides afforded the *N*-triazolyl maleimide in yields ranging from 63% to 83% (Table 2, entries 3 and 10–12, respectively). It was observed that the reaction temperature suddenly rose (rt to 40 °C) when the base was added and a bluish ring appeared that changed to green during the course of the reaction. The ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR and mass spectral data were all in agreement with the structure of the compounds.

In order to gain further insight into the reaction, *in situ* Fourier transform infrared spectroscopy (FT-IR)[29] was used to monitor the reaction. During the experiment, a band of C=N at 1573 cm^{-1} was observed that started to increase until its formation reached a maximum at 40 min. The C=C stretch band is at 1647 cm^{-1} and the C=C-H bending vibrations were at 967 cm^{-1}, 813 cm^{-1} and 779 cm^{-1}. So triazole formation and removal of the acetate group were accomplished in 40 min (Fig. 2).

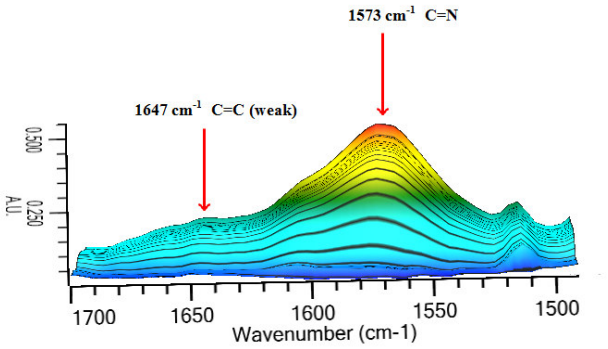
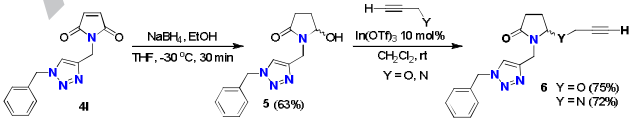


Figure 2. Three-dimensional plot of the IR monitoring

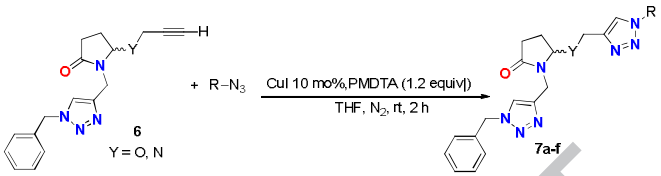
Next, *N*-triazolyl maleimide **4l** was successively treated with sodium borohydride in ethanol/THF at -30 °C for 30 min leading to **5**, that was found as the only product,[30] and then propargyl alcohol or propargyl amine were added to the acyliminium ion catalyzed by In(OTf)$_3$ to afford the respective *N*-triazolyl-5-propargyl pyrrolidones[31] (**6**). (Scheme 2).

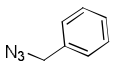
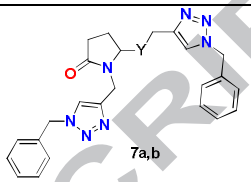
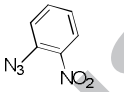
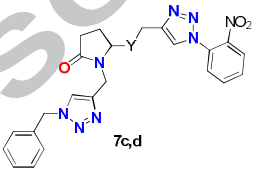
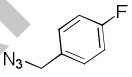
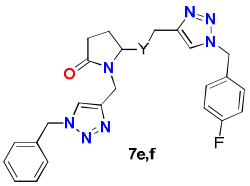


Scheme 2. Addition reaction of propargyl alcohol or propargyl amine

The standard reaction[32] was carried out with *N*-triazolyl-5-propargyl pyrrolidones (**6**) (1.0 mmol), 10 mol% CuI, PMDTA (1.2 equiv), 1.2 equiv of organic azide and THF (5 mL) as solvent. Using these conditions, the products were obtained in yields ranging from 67% to 77% (Table 3).

Table 3. Synthesis of *N*-1,2,3-triazolyl-5-(1,2,3-triazolyl)pyrrolidones



Entry	Azide	Product	Yield (%)
1		 7a,b	**a** = Y = O = 72 **b** = Y = N = 67
2		 7c,d	**c** = Y = O = 77 **d** = Y = N = 71
3		 7e,f	**e** = Y = O = 68 **f** = Y = N = 67

Conclusion

In conclusion, we have developed an efficient two step one-pot elimination and click chemistry reaction of *N*-propargyl imide with aromatic- and alkyl azides promoted by CuI using PMDTA as base, which allows the assembly of a wide range of functionalized *N*-triazolyl maleimides. Next, the *N*-triazolyl maleimides were submitted to the addition of propargyl alcohol and propargyl amines through the *N*-acyliminum ion catalyzed by Lewis acid, and then converted into the corresponding *N*-triazolyl-5-triazolyl pyrrolidones in moderate to good yields.

Both transformations, of *N*-triazole maleimides and *N*-triazole-5-triazolyl pyrrolidones, are operationally simple, the substrate scope is wide, and the starting materials are readily available.

This study increases our understanding of the character of the click chemistry reaction and the *N*-acyliminum ion but also sheds important light on how to further expand its scope and utility.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found in the online version. Experimental details and analytical data for all new compounds, as well as the ^{1}H and ^{13}C NMR spectra, are presented therein.

References and notes

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28.**General procedure**: 1-((1-benzyl-1*H*-1,2,3-triazol-5-yl)methyl)-1*H*-pyrrole-2,5-dione (**4l**) - To a solution of the 2,5-dioxo-1-(prop-2-yn-1-yl)pyrrolidin-3-yl acetate (**3l**) (195.05 mg, 1.0 mmol, 1.0 equiv) in THF (5 mL) at 25 °C under a nitrogen atmosphere were added benzyl azide (160 mg, 1.2 mmol, 1.2 equiv) and CuI (57 mg, 0.3 mmol, 30 mol%). TMDTA (208 mg, 1.2 mmol, 1.2 equiv.) was then added dropwise. The reaction mixture was stirred at room temperature for 1 h. TLC analysis revealed no starting material. Next, the reaction was quenched with CH_2Cl_2 (20 mL) and the organic phase was washed with saturated NH_4Cl (10 mL) and then dried over $MgSO_4$. Evaporation under reduced pressure followed by column chromatography on silica gel (40% ethyl acetate in hexanes) afforded the product as a white solid. **1-((1-benzyl-1H-1,2,3-triazol-5-yl)methyl)-1*H*-pyrrole-2,5-dione :** The product was obtained as a beige solid, m.p. 115-116 °C. Yield (224 mg, 83%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.67 (s, 2H), 5.37 (s, 2H), 6.59 (s, 2H), 7.25-7.26 (m, 5H), 7.37 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 34.2, 54.1, 123.0, 128.1-129.1(7C), 134.2 (2C), 170.0 (2C); HRMS calcd for $C_{14}H_{12}N_4O_2$ (M+Na): 291.0858; found: 291.0846.

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32.**General procedure**: 5-((1-benzyl-1*H*-1,2,3-triazol-5-yl)methoxy)-1-((1-benzyl-1*H*-1,2,3-triazol-5-yl)methyl)-1,5-dihydro-2H-pyrrol-2-one (**7a**) - To a solution of the 1-((1-benzyl-1*H*-1,2,3-triazol-5-yl)methyl)-5-(prop-2-yn-1-yloxy)-1,5-dihydro-2*H*-pyrrol-2-one (308.13 mg, 1.0 mmol, 1.0 equiv.) in THF (5 mL) at 25 °C under a nitrogen atmosphere were added benzyl azide (160 mg, 1.2 mmol, 1.2 equiv.) and CuI (19 mg, 0.1 mmol, 10 mol-%). PMDTA (208 mg, 1.2 mmol, 1.2 equiv.) was then added dropwise. The reaction mixture was stirred at room temperature for 1 h. TLC analysis revealed no starting material. Next, the reaction was quenched with CH_2Cl_2 (20 mL) and the organic phase was washed with saturated NH_4Cl (10 mL) and then dried over $MgSO_4$. Evaporation under reduced pressure followed by column chromatography on silica gel (70% ethyl acetate in hexanes) afforded the product as a colorless oil. **5-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)pyrrolidin-2-one:** The product was obtained as a viscous yellow oil. Yield (321 mg, 72%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.09(t, *J* = 7.5, 7.8 Hz, 2H), 2.30(t, *J* = 7.8, 8.4 Hz, 2H), 4.20 (s, 4H), 4.62 (s, 2H), 5.32 (s, 3H), 7.20-7.23 (m, 10H), 7.41 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 26.5, 26.9, 52.8, 53.5 (2C), 67.2, 91.2, 121.8, 126.8, 126.9 (2C), 127.0 (2C), 127.5 (2C), 127.8, 133.4, 134.4 (2C), 141.1 (2C), 176.5 (C); HRMS calcd for $C_{24}H_{25}N_7O_2$ (M+Na): 466.1967; found: 466.1975.