Tetrahedron Letters 52 (2011) 4256–4261

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 5-alkynyl-2,2,6-trimethyl-1,3-dioxin-4-ones and 1,4-disubstituted-1,2,3-triazoles

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ARTICLE INFO

Article history:
Received 15 March 2011
Accepted 18 April 2011
Available online 24 April 2011

Keywords:
Suzuki–Miyaura
2,2,6-Trimethyl-5-iodo-1,3-dioxin-4-one
Alkynyltrifluoroborates
Cross-coupling reaction
1,4-Disubstituted-1,2,3-triazoles

ABSTRACT

Herein we report an approach to the formation of 5-alkynyl-1,3-dioxin-4-ones using Suzuki–Miyaura cross-coupling reaction of potassium alkynyltrifluoroborate salts with 2,2,6-trimethyl-5-iodo-1,3-dioxin-4-one. The resulting 5-ethynyltrimethylsilyl-1,3-dioxin-4-ones obtained through the Sonogashira reaction were further reacted in a Cu(I)-catalyzed Huisgen azide–alkyne 1,3-dipolar cycloaddition to form functionalized 1,4-disubstituted-1,2,3-triazoles in good yields, using mild conditions and ultrasonic radiation to expedite the reaction.

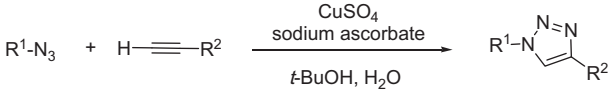
1. Introduction

Transition metal-catalyzed cross-coupling reactions have become ubiquitous in modern organic synthesis.[1] Carbon–carbon bond-formation processes, which are typically mediated by nickel, palladium, iron, or copper catalysts, have become commonplace both in academic research and in the pharmaceutical industry. Of these carbon–carbon bond-forming reactions, the Suzuki–Miyaura cross-coupling reaction[2] is distinguished because the boron compounds have many significant advantages over the other organometallic reagents used in these types of reactions. The high versatility and high functional-group tolerance of the Suzuki–Miyaura reaction, as well as the recent advances in the coupling of sterically hindered substrates, have increased the utility of the reaction in the syntheses of complicated and sensitive molecules, including pharmaceutical compounds such as Diovan and Cozaar.[3]

Originally discovered by Huisgen in the 1960's,[4] the 1,3-dipolar cycloaddition reaction between acetylenes and azides was revisited and expanded by Sharpless and others during the development of 'click chemistry'.[5]

Recently Fokin and co-workers reported the synthesis of 1,5-diarylsubstituted 1,2,3-triazoles from aryl azides and terminal alkynes in DMSO using a catalytic amount of tetraalkylammonium hydroxide.[6]

The concept of 'click chemistry' takes advantage of a wide range of modular, stereospecific reactions and gives products in high yields without forming offensive byproducts.[5] These reactions have already been used to efficiently access useful new compounds. Among these 'click chemistry' reactions, the Huisgen [3+2] cycloaddition has enabled the reliable synthesis of a plethora of new compounds, which has been very useful in drug discovery. This Cu(I) catalyzed reaction has been largely successful because it provides virtually quantitative yields and because the robust reaction is not sensitive to solvents and functional groups. The use of Cu(I) is superior to that of other metal catalysts in this reaction because it is significantly less expensive and easier to handle than other catalysts described to accomplish the same transformation. Most of the other metal catalyzed reactions involve the reduction of stable Cu(II) sources, such as $CuSO_4$, and use sodium salts or the comproportionation of Cu(II)/Cu(0) species (Scheme 1).



Scheme 1. The Huisgen [3+2] cycloaddition.

The availability of a reliable reaction to form azoles has lead to advances in the applications of azoles in medicinal chemistry, chemical biology, and materials science.[7]

The regioselectivity of the reaction coupled with its modularity, high yields and simple conditions and purification techniques have lead to the use of 1,3-dipolar cycloaddition reactions between alkynes and azides in numerous syntheses of modified nucleosides and oligonucleotides that have a broad range of important applications.[8]

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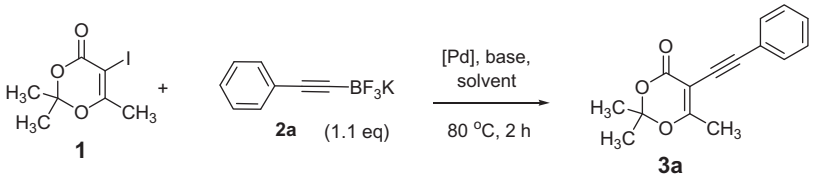
doi:10.1016/j.tetlet.2011.04.072

Table 1
Optimization of the conditions for the Suzuki–Miyaura cross-coupling reaction between **1** and **2a**



Entry	Catalyst[a]	Base[b]	Solvent	Yield[c] (%)
1	$Pd(AcO)_2$	K_2CO_3	1,4-Dioxane/H_2O[d]	42
2	$Pd_2(dba)_3$	K_2CO_3	1,4-Dioxane/H_2O[d]	51
3	$Pd(Ph_3P)_4$	K_2CO_3	1,4-Dioxane/H_2O[d]	64
4	$PdCl_2$	K_2CO_3	1,4-Dioxane/H_2O[d]	72
5	$PdCl_2$	Cs_2CO_3	1,4-Dioxane/H_2O[d]	51
6	$PdCl_2$	Et_3N	1,4-Dioxane/H_2O[d]	47
7	$PdCl_2$	*i*-Pr_2NEt	1,4-Dioxane/H_2O[d]	32
8	$PdCl_2$	K_3PO_4	1,4-Dioxane/H_2O[d]	43
9	$PdCl_2$	K_2CO_3	THF/H_2O (3:1)	78
10	$PdCl_2$	K_2CO_3	CH_3OH	31

[a] 1.0 mol % of palladium catalyst.
[b] 1.5 equiv of base.
[c] Isolated yield of pure product.
[d] 1,4-Dioxane/H_2O ratio: 2:1.

2. Results and discussion

As part of our ongoing research in the chemistry of potassium organotrifluoroborate salts,[9] Cu(I) alkyne–azide Huisgen [3+2] cycloaddition, 5-halo-1,3-dioxin-4-ones, and the potential use of these compounds as intermediates in organic synthesis, we report an efficient method for the synthesis of 5-alkynyl-1,3-dioxin-4-one compounds by the Suzuki–Miyaura palladium-catalyzed cross-coupling reaction of 5-iodo-1,3-dioxin-4-one and potassium aryltrifluoroborate salts. The product of the coupling of potassium ethynyltrimethylsilyltrifluoroborate and 5-iodo-1,3-dioxin-4-one, obtained using the Sonogashira coupling reaction, was then used in a series of Huisgen [3+2] cycloaddition reactions, mediated by ultrasound, to form the respective 1,2,3-triazole substituted 1,3-dioxin-4-ones very quickly. The Letter ends with two ring-opening deprotection reactions[9f] of the 1,2,3-triazole substituted dioxin-4-ones to demonstrate the versatility of the substrate and the reactions summarized herein.

The functionalization of position 5 of 1,3-dioxin-4-ones with an electrophile forms compounds that are potentially useful as pharmaceuticals and agrochemical intermediates.[10] The starting material for these reactions was formed by the iodination of commercially available 2,2,6-trimethyl-1,3-dioxin-4-one with *N*-iodosuccinimide (NIS) in acetic acid and protected from light to form 5-iodo-1,3-dioxin-4-one 1 in 68% isolated yield.

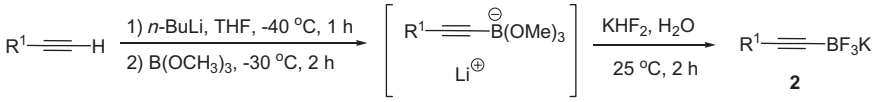
The potassium alkynyltrifluoroborate salts (**2a**–**h**) were prepared from organolithium reagents as described in the literature[2] (Scheme 2). The lithium acetylides were formed by adding a 1.6 M solution of *n*-BuLi in hexanes to a solution of the acetylene in THF at −40 °C and allowing the mixture to react for 1 h. The lithium acetylides were then treated with $B(OCH_3)_3$ for 2 h at −30 °C to generate lithium acetylide trimethylborates, after which the products were treated with a saturated aqueous solution of potassium hydrogen difluoride (KHF_2). After the solvents were removed, the crude salt was recrystallized in an acetone/diethyl ether mixture to form the corresponding potassium alkynyl trifluoroborate **2a**–**h**. These reactions gave good yields and were relatively easy to perform.

These potassium alkynyltrifluoroborates were then used in the development of a Suzuki–Miyaura reaction. Our initial studies were focused on the optimization of the reaction conditions for the palladium-catalyzed cross-coupling of potassium alkynyl trifluoroborates **2** with 5-iodo-1,3-dioxin-4-one **1**. The optimization was done by screening the reaction conditions, the results of which are summarized in Table 1. During the screening process, several palladium catalysts including $Pd(PPh_3)_4$, $Pd(AcO)_2$, $Pd_2(dba)_3$ and $PdCl_2$ were tested, and a variety of different bases (Et_3N, *i*-Pr_2NEt, K_2CO_3, Cs_2CO_3 and K_3PO_4) and different solvent systems (MeOH, EtOH, *i*-PrOH, THF, DME, and 1,4-dioxane) under both anhydrous and aqueous conditions were evaluated.

The use of alcohol as solvent decreased the yield of the coupling product (Table 1, entry 10). This is probably because the presence of the alcohol at the required temperature for the reaction can promote the ring-opening reaction of the 1,3-dioxin-4-one, which can compete with the Suzuki–Miyaura cross-coupling reaction.

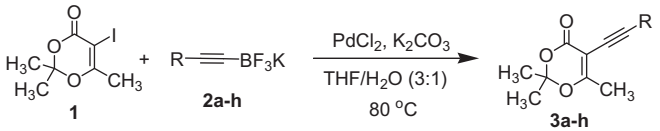
The optimal conditions for the cross-coupling reaction found were treating 1.1 equiv of potassium phenylethynyl trifluoroborate **2a** (1.1 mmol) with 1.5 equiv of K_2CO_3 in 3 mL of degassed THF/H_2O (3:1). To this solution, 2.0 mol % of $PdCl_2$ and 1.0 equiv of 5-iodo-1,3-dioxin-4-one **1** were added and the reaction mixture was stirred vigorously for 3 h at 80 °C (Table 2).

As is shown in Table 2, the coupling reactions of potassium alkynyl trifloroborates **2** gave only moderate to low yields, with a few exceptions.[11] Aromatic substrates (**2a**–**c**,**f**,**g**) (Table 2, entries 1–3) formed their corresponding products in relatively good yields, while aliphatic substrates (**2d**,**e**) (Table 2, entries 4 and 5) gave the

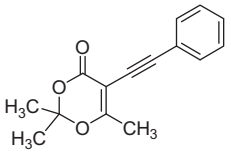
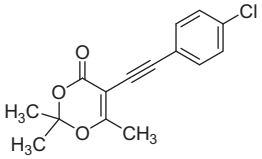
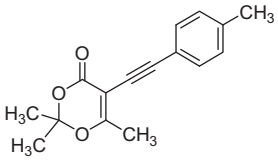
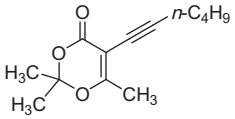
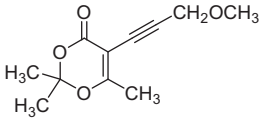
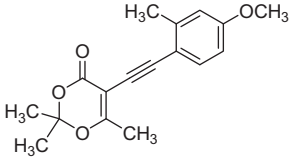
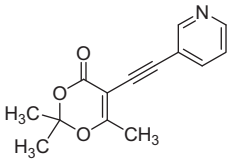
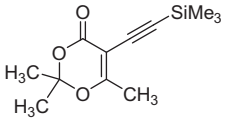


Scheme 2. Synthesis of potassium alkynyl trifluoroborates **2**.

Table 2
Cross-coupling reactions of 5-iodo-1,3-dioxin-4-one **1** with potassium alkynyltrifluoroborates **3a–l**



1 **2a-h** **3a-h**

Entry	R[1a]	Reaction time (h)	Product (**3**)	Yield[b] (%)
1	Ph (**2a**)	3	 **3a**	78
2	4-ClC_6H_4 (**2b**)	4	 **3b**	65
3	4-MeC_6H_4 (**2c**)	3	 **3c**	72
4	n-C_4H_9 (**2d**)	6	 **3d**	47
5	$MeOCH_2$ (**2e**)	6	 **3e**	53
6	2-$Me_4MeOC_6H_4$ (**2f**)	4	 **3f**	63
7	3-C_5H_5N (**2g**)	6	 **3g**	61
8	Me_3Si (**2h**)	6	 **3h**	–

[a] 1.1 equiv of R^1–C≡C–BF_3K.
[b] Isolated yield of pure product.

products in more moderate yields, with longer reaction times. The yields of all of these reactions could likely be improved by a more detailed study of this reaction, including further optimization of the reaction medium, the catalyst and the substrates.

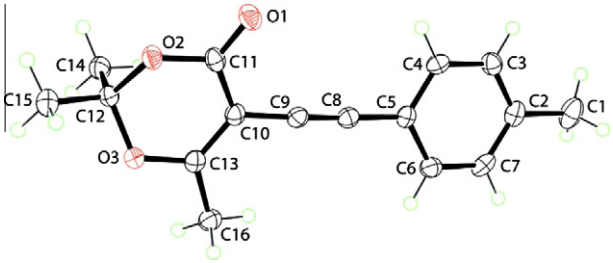
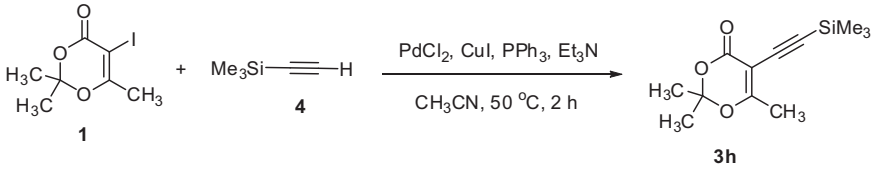


Figure 1. Thermal ellipsoid plot of 5-(*p*-tolyl-ethynyl)-2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **3c**.

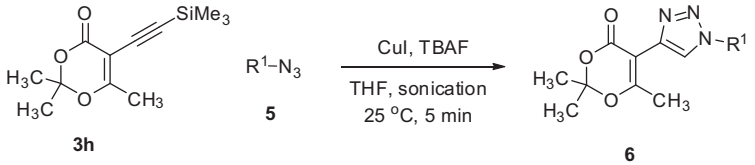
Products **3a–h** were analyzed by ^{1}H and ^{13}C NMR, and their physical data are in full agreement with their assigned structures. Crystallographic analysis of product **3c** was also performed, and its thermal ellipsoid plot is show in Figure 1. Compound **3c** was recrystallized in anhydrous methanol prior to its crystallographic analysis (Fig. 1).[12]

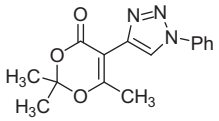
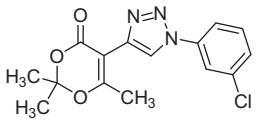
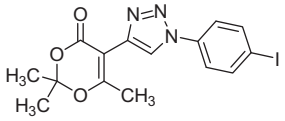
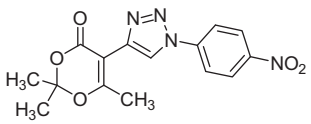
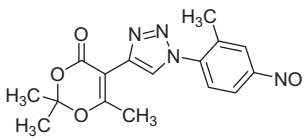
Anomalous to the reasonably successful results found for both aliphatic and aromatic trifluoroborate salts (Table 2, entries 1–7), the Suzuki–Miyaura cross-coupling reaction of the trimethylsilyl alkynyltrifluoroborate salt (**2h**) with the 5-iodo-1,3-dioxin-4-one (**1**) was completely unsuccessful. The formation of this product re-



Scheme 3. Sonogashira coupling reaction of 5-iodo-1,3-dioxin-4-one.

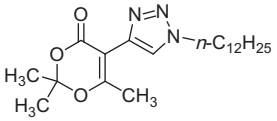
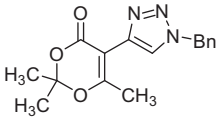
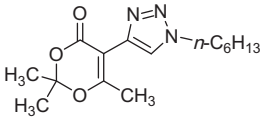
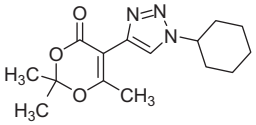
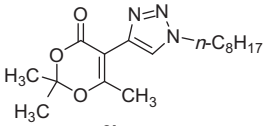
Table 3
Huisgen 1,3-dipolar cycloaddition of 5-alkynyl-1,3-dioxin-4-one **3h** with azides **5a–j**



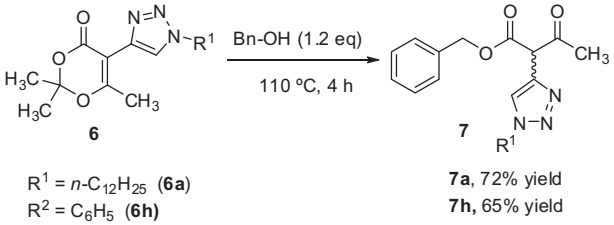
Entry	$R^1–N_3$[a] (**5**)	Reaction time (min)	Product (**6**)	Yield[b] (%)
1	$C_6H_5N_3$	5	 **6a**	80
2	3-$ClC_6H_4N_3$ (**5b**)	5	 **6b**	73
3	4-$IC_6H_4N_3$ (**5c**)	5	 **6c**	85
4	4-$O_2NC_6H_4N_3$ (**5d**)	4	 **6d**	70
5	4-O_2N,2-Me-$C_6H_4N_3$ (**5e**)	4	 **6e**	81

(*continued on next page*)

Table 3 (*continued*)

Entry	R^1–N_3[a] (**5**)	Reaction time (min)	Product (**6**)	Yield[b] (%)
6	*n*-$C_{12}H_{25}N_3$ (**5f**)	70	 **6f**	75
7	$C_6H_5CH_2N_3$ (**5g**)	50	 **6g**	84
8	*n*-$C_6H_{13}N_3$ (**5h**)	60	 **6h**	79
9	*c*-$C_6H_{11}N_3$ (**5i**)	80	 **6i**	78
10	*n*-$C_8H_{17}N_3$ (**5j**)	50	 **6j**	74

[a] 1.2 equiv of R^1–N_3.
[b] Isolated yield of pure product.



Scheme 4. Ring-opening reactions of 1,2,3-triazoles.

quired the use of the related Sonogashira cross-coupling reaction, which was performed according to the conditions specified in the literature.[13] The Sonogashira cross-coupling reaction formed product **3h** with an isolated yield of 56% (Scheme 3).

Product **3h** was converted via the Huisgen 1,3-dipolar cycloaddition and azides (**5a**–**j**) in the corresponding 1,4-disubstituted-1,2,3-triazole compounds (**6a**–**j**) by a simple 'click chemistry' reaction mediated by a copper catalyst as is shown in Table 3.

While this reaction is generally sluggish, the reaction time was significantly reduced by sonicating the reaction,[14] as is shown in the literature.[10] The short reaction time associated with this version of the Huisgen reaction under ultrasonic waves makes the methodology much more synthetically and industrially useful.

Though many different substitutions were tested, the results showed no preference to any specific functional groups on the azide reagents (**5a**–**j**). While some variation is seen in the yields, all of the yields were reasonably good. It seems that the aromatic azides had slightly higher yields than nonaromatic ones, although there are exceptions.

After the highly functionalized triazoles (**5a**–**j**) were obtained through the 1,3-dipolar cycloaddition reaction, a ring-opening reaction was performed on two of the products to demonstrate the versatility and applicability of these triazole compounds. These ring-opening reactions converted the 1,4-disubstitutes-1,3-dioxin-4-ones into their corresponding α-substituted 1,3-dicarbonyl compounds, which have great applicability in the field of synthetic organic chemistry, as they can be used in variations of the acetoacetic ester synthesis.

The ring-opening reactions[9f] were run under simple conditions, by combining an alcohol with the 1,4-disusbstituted-1,2,3-triazole in the absence of an external solvent, and heating the reaction to 110 °C under nitrogen atmosphere (Scheme 4).

The yields of these deprotections were moderate to good,[15] depending on the substitutions on the triazole ring. While the two examples of these reactions are representative of the many applications possible using 2,2,6-trimethyl-1,3-dioxin-4-one substrate, further investigations are required to fully understand any trends in yields based on the various R groups, and to fully optimize these reaction conditions.

3. Conclusion

We have shown the wide versatility and reasonable yield of the optimized conditions for the Suzuki–Miyaura cross-coupling reaction of potassium alkynyl trifluoroborates with 1,3-dioxin-4-ones. This methodology is preferred over many other organometallic-compound-based cross-coupling reactions because potassium organotrifluoroborate salts are readily available, very stabile, nontoxic, mildly nucleophilic in character, because they have a unique compatibility with aqueous media. It was observed that while

Suzuki–Miyaura reaction did not work for all examples it can be substituted by the Sonogashira reaction giving highly functionalized 1,4-disubstituted-1,2,3-triazole-containing compounds.

The short reaction time associated with our variation on the 1,3-dipolar cycloaddition reaction using ultrasound waves makes the methodology much more synthetically useful.

Acknowledgments

The authors would like to acknowledge Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq 300.613/2007-5) and Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP 06/50190-7, 07/02382-7 and 07/59404-2) for their financial support.

Supplementary data

Supplementary data (experimental procedures, spectral data and copies of spectra for all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.072.

References and notes

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11. General procedure for the cross-coupling reaction of potassium alkynyltrifluoroborates with 5-iodo-2,2,6-trimethyl-1,3-dioxin-4-one. To a solution of the alkynyl potassium trifluoroborate (1.1 mmol, 1.1 equiv) in degassed THF/water (3:1, 3 mL) was added solid K_2CO_3 (1.5 mmol, 1.5 equiv). The mixture was stirred vigorously for 1 min under a nitrogen atmosphere after which $PdCl_2$ (0.01 mmol, 1.0 mol %) was added, followed by 5-iodo-2,2,6-trimethyl-1,3-dioxin-2-one (**1**) (268 mg, 1.0 mmol, 1.0 equiv). The reaction was heated to 80 °C and stirred vigorously, while being monitored by TLC until the starting material had been completely consumed. The reaction mixture was cooled to room temperature and was then extracted from the reaction mixture using ethyl acetate (20 mL). Additional product was extracted from the aqueous phase with ethyl acetate (3 × 15 mL), and the combined organic phases were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes/ethyl acetate, 10:1) to afford the product.
5-Phenylethynyl-2,2,6-trimethyl-4H-1,3-dioxin-4-one (**3a**). Following the general procedure: 78% yield, white solid, mp = 51–52 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78 (s, 6H), 1.98 (s, 3H), 7.28–7.43 (m, 3H), 7.84 (d, J = 8.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 25.9, 87.8, 92.7, 101.1, 104.0, 128.4, 128.6, 129.3, 133.2, 163.0, 168.8. GC/MS (relative intensity): m/z 242 (10) [M$^+$], 184 (45), 156 (34), 77 (20), 43 (100).
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14. General procedure for the cross-coupling reaction of potassium alkynyltrifluoroborates with 5-iodo-2,2,6-trimethyl-1,3-dioxin-4-one. To a solution of the alkynyl potassium trifluoroborate (1.1 mmol, 1.1 equiv) in degassed THF/water (3:1, 3 mL) was added solid K_2CO_3 (1.5 mmol, 1.5 equiv). The mixture was stirred vigorously for 1 min under a nitrogen atmosphere after which $PdCl_2$ (0.01 mmol, 1.0 mol %) was added, followed by 5-iodo-2,2,6-trimethyl-1,3-dioxin-2-one (**1**) (268 mg, 1.0 mmol, 1.0 equiv). The reaction was heated to 80 °C and stirred vigorously, while being monitored by TLC until the starting material had been completely consumed. The reaction mixture was cooled to room temperature and was then extracted from the reaction mixture using ethyl acetate (20 mL). Additional product was extracted from the aqueous phase with ethyl acetate (3 × 15 mL), and the combined organic phases were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes/ethyl acetate, 10:1) to afford the product.
5-Phenylethynyl-2,2,6-trimethyl-4H-1,3-dioxin-4-one (**3a**). Following the general procedure: 78% yield, white solid, mp = 51–52 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78 (s, 6H), 1.98 (s, 3H), 7.28–7.43 (m, 3H), 7.84 (d, J = 8.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 25.9, 87.8, 92.7, 101.1, 104.0, 128.4, 128.6, 129.3, 133.2, 163.0, 168.8. GC/MS (relative intensity): m/z 242 (10) [M$^+$], 184 (45), 156 (34), 77 (20), 43 (100).
15. General procedure for reaction of 5-(1-phenyl-1,2,3-triazol-4-yl)-2,2,6-trimethyl-1,3-dioxin-4-one (**6a**) with benzyl Alcohol. The synthesis of benzyl-3-oxo-2-(1-phenyl-1*H*-1,2,3-triazol-4-yl)butanoate (**7a**) is representative. A solution of 2,2,6-trimethyl-5-(1-phenyl-1H-1,2,3-triazol-4-yl)-*4H*-1,3-dioxin-4-one (**6a**) (142.5 mg, 0.5 mmol, 1.0 equiv) and benzyl alcohol (65 mg, 0.6 mmol, 1.2 equiv) was stirred well under an atmosphere of nitrogen for 8 h at 110 °C. The crude product was purified by column chromatography on a silica column (hexane/ethyl acetate, 95:5), giving the pure benzyl 3-oxo-2-(1-phenyl-*1H*-1,2,3-triazol-4-yl)butanoate with a 65% yield.
Benzyl-3-oxo-2-(1-phenyl-1*H*-1,2,3-triazol-4-yl)butanoate (**7a**). 65% yield, yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 4.27 (s, 1H), 5.52 (s, 2H), 7.27–7.54 (m, 8H), 7.76–7.80 (m, 2H), 8.52 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 61.1, 71.1, 120.4 (2C), 121.7, 128.8 (2C), 129.4 (2C), 129.7, 130.9 (2C), 130.9, 137.0, 140.5, 167.9, 200.5.